VOLUME 19 NUMBER 2

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AUGUST, 1929

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, July 10, 1925, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized July 29, 1920.

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ARCHIVES OF SURGERY

VOLUME 19 AUGUST, 1929 NUMBER 2

OSTEITIS FIBROSA AND GIANT CELL TUMOR *

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AND

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WITH FOREWORD BY

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FOREWORD

First, I would like to acknowledge our indebtedness to Mrs. Carl Joerissen, of Washington and Paris, and to those former patients and friends who contributed to the fund that made this research possible.

These two research fellows, Dr. Charles F. Geschickter and Dr. Murray M. Copeland, in the Surgical Pathological Laboratory of the Johns Hopkins University, began an independent study of multiple myeloma during the early spring of 1927, their senior year in the medical school, and continued their research in the laboratory and in the library. These studies were published in the ARCHIVES OF SURGERY in the April, 1928, issue, page 807.

During this time, they reviewed the entire collection of bone material in the laboratory, and thus prepared themselves for the more intensive study of all lesions of bone and all benign and malignant connective tissue tumors, beginning in July, 1928. Two papers are ready for publication; this one on the nature of osteitis fibrosa and giant cell tumor, and a second one, on the round cell sarcoma of bone, often of alveolar character, which is now grouped under the name of Ewing's sarcoma. These two papers, therefore, contrast the benign type of bone lesions with the malignant tumors. A third paper on osteogenic sarcoma is in process of preparation, and in this third contribution, which is the result of six months' research by the authors, an attempt will be made to present the differential diagnosis of the different types of benign and malignant tumors of bone and soft parts clinically, roentgenographically and microscopically—a presentation that has never been thoroughly made before.

It is only just to record that these papers present the personal views of these two students, and anything original that is presented should be

* Submitted for publication, Dec. 17, 1928.

* Publication aided by grant from the fund of the Hartley Corporation.

* Illustrations by Mr. Herman Schapiro.

credited to them. All that the laboratory did was to furnish them with the material for the study. It is my opinion that in these papers they have pr ed new, interesting and, I trust, correct pictures both of the natu of osteitis fibrosa and the giant cell tumor and of the nature of sarcoma, which not only will be valuable in the practical diagnosis and treatment of these lesions of bone in their earliest stage, but will form a basis for future progressive investigation.

I do not wish to anticipate in this introduction any of the statements made in the paper; I wish only to emphasize here and there some of the more important conclusions.

MALIGNANT GIANT CELL TUMOR

Although the authors are firmly convinced that osteitis fibrosa and the giant cell tumor are either identical or of natures closely allied, they have been unable, in the series of cases studied or in the literature, to find a proved case of malignancy arising in the benign bone lesion called osteitis fibrosa, which is situated in the shaft of bones of young persons. In spite of the fact that the age incidence of Ewing's sarcoma and of osteogenic sarcoma is the same as that of osteitis fibrosa, except that more cases of the malignant type are observed in persons more than 20 years of age, there is no evidence that these sarcomas develop in bone, the seat of osteitis fibrosa.

In the literature, there seem to be reported a few authentic and verified cases in which malignancy developed in a tumor involving the epiphysis of an adult which must be looked on as a benign giant cell tumor; that is, later in this benign giant cell tumor tissue, malignant sarcoma cells appeared, and gave rise to metastases in the lungs, in which also the giant cells were present. Together we studied all the cases in the literature and all the cases in our own series, and this research will be published later.

In the cases in which we have the material for study there occurred but one death from metastasis from a possible giant cell tumor of the epiphysis. In this case, the restudy of the sections of the original tumor classified it with the malignant variant of the giant cell tumor, of which we have had eight cases and only one of which metastasized. The other seven reacted as any giant cell tumor does. I think we can say here in anticipation of this publication that the danger of malignancy in a central tumor of the epiphysis which microscopically belongs to the giant cell group is so remote that one is justified in the conservative treatment by curetting or by x-ray radiation.

The histologic studies and illustrations presented in this paper by Geschickter and Copeland, I hope, will give surgical pathologists and pathologists a greater confidence in their ability to diagnose the giant cell tumor and to place it in the benign group. I have just visited a modern and thoroughly scientific surgical clinic in which the chief

surgeon is a well-trained surgical pathologist. Nevertheless, he presented to me a case in which, because of the microscopic sections, he feared malignancy in a giant cell tumor. The case offered a clearcut clinical and x-ray picture of a central tumor with an intact bone shell involving a condyle, or a little more, of the lower end of the femur. There had been an injury with a pathologic fracture, which had healed, and the curettement of the central tumor had followed some weeks after the healing of the fracture. The x-ray photograph therefore, showed a little formation of bone outside of the bone shell, and the microscopic section pictured in addition to the typical giant cell tumor, shown in the accompanying illustrations, young granulation tissue with cells of the morphologic type of the sarcoma cell, near islands of new bone formation, the result of the fracture. Unfortunately, the fear of malignancy in the giant cell tumor is still too prevalent, and only studies of this character will ultimately allay that fear. There should not be any difficulty in differentiating the variations in the typical giant cell tumor from the malignant variant (fig. A) and the fully developed sarcoma (fig. 21). It is important to emphasize here that the malignant tumors of the epiphysis are sarcoma developing in chondroma or myxoma. Ewing's tumor involves the epiphysis only secondarily from the shaft. The osteogenic sarcoma involving the epiphysis has an entirely different x-ray and microscopic picture. The metastatic tumor of the epiphysis is rare, but there should be no difficulty in differentiating giant cell tumor from metastatic carcinoma. The majority of bone aneurysms recorded in the literature were simply blood cysts with zones of giant cell tumor tissue in the epiphysis. In our series of cases there are but two bone aneurysms in which the tissue outside of the blood cavity, lining the bone shell, showed no evidence of the giant cell tumor. We have not observed a malignant aneurysm for more than twenty-five years,* and the tissue in the two cases is not sufficiently well preserved to allow an exact histologic diagnosis. Both these patients died of metastases. Their tumors may belong to the group we have designated as the malignant variant of the giant cell tumor, of which we have eight cases, in one of which death was due to metastasis.

This malignant variant of the giant cell tumor (fig. A), as stated before, can be easily recognized at the biopsy from the frozen section. I have no evidence that it should be treated any differently. The facts are these: One curetted in the upper end of the humerus eight years ago has not recurred; another has not recurred in three years; two have not

* Since this article was written, I have observed a third case of bone aneurysm in a child, aged 12. The roentgenograms showed a defect in the shaft similar to bone cyst, but the bone destruction suggested malignancy. At exploration there was a blood cyst surrounded by tumor tissue, microscopically osteogenic sarcoma. This roentgenogram of an osteogenic sarcoma resembles that of a bone cyst more than any other sarcoma that we have observed.

recurred on recent observations of one and two years since the curetting. In one case in which an amputation was done in 1905, the patient was living twenty-three years later. Two recurred. One was in the lower end of the fibula, which was resected in a few months, and the patient at the time of writing has been well for five years. The second was in the lower end of the femur; it recurred two years after curetting. The limb was amputated and the patient is living at the time of writing, six years afterward.

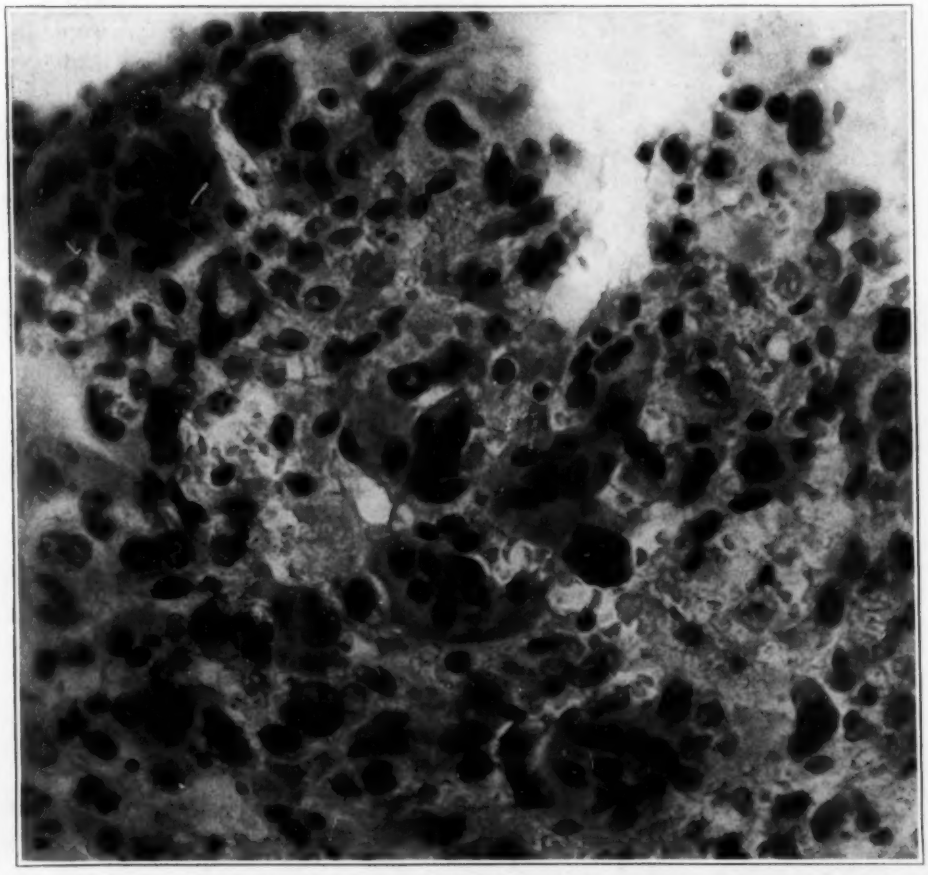

Fig. *A*.—The malignant variant of the giant cell tumor. Four large and several small giant cells are seen in the field. Among the small round cells of the stroma are larger cells with more cytoplasm and vesicular nuclei simulating sarcoma.

I am rather inclined to the view that if one finds a malignant variant of the giant cell tumor in the frozen section, it is wiser to resect and do a transplantation of bone, except in the lower end of the femur or the upper end of the tibia, where resection does not give as useful a limb as amputation and an artificial leg. Here one can try thorough curetting with chemical and thermal cauterization and irradiation to be followed by amputation if the tumor recurs.

To repeat, this small group of eight cases of the malignant variant of the giant cell tumor contains our only case of a supposed giant cell tumor which metastasized, and also shows a larger percentage of recurrences.

These eight cases of the malignant variant among 226 giant cell tumors were recognized by the authors when they first studied the microscopic sections without any knowledge of previous diagnosis or of clinical results.

RECURRENCE IN THE GIANT CELL TUMOR AFTER CURETTING

We have no record of a recurrence after resection. The only record of a recurrence in the stump after amputation was found in the literature, and in this instance the patient died of metastasis. The observation was made by Finch and Gleave of England and was reported in the *Journal of Pathology and Bacteriology* in the October, 1926, issue, page 329. We have thirty-two cases of recurrence after curetting. I presented the results of an investigation of the latter before the American Orthopedic Association in May, 1928, and the paper will be published in the *Journal of Bone and Joint Surgery*. From my studies, the chief factors in recurrence after curetting are: first, incomplete removal of the tumor, either because of hemorrhage or because of the inexperience of the operator; second, the failure to use chemical or thermal cauterization; third, attempting curettement when the bone shell is perforated or too much destroyed. There has been recurrence in the group with the latter condition in spite of thermal and chemical cauterization and in spite of preoperative and postoperative irradiation. I, personally, have had two cases which I have made the basis for my communication. The authors feel that in patients of more than 30 years of age, the danger of recurrence is greater than in younger persons, because the bone shell has lost its power to react and ossify.

RADIATION IN THE TREATMENT OF GIANT CELL TUMORS

Since my publication in the *Journal of Radiology* in March, 1920, I have repeated in every publication that it is wiser to put the doubtful bone lesions at rest and give x-ray treatment than to perform a biopsy, unless the operator or his pathologist has sufficient experience to make a differential diagnosis from the frozen section, and the patient is willing to have an amputation should the tumor prove malignant. Each year's experience confirms the truth of this. It is far safer to submit the x-ray photographs to others for help in diagnosis, employing radiation while waiting, than to perform a biopsy and send the section around for diagnosis.

In the past two years, the evidence has been increasing that persistent irradiation with x-rays or radium ultimately, in many instances, controls the giant cell growth. The tumor itself shrinks, and the x-ray

photograph shows increasing ossification. We are not yet prepared to make an exact comparison of the results after irradiation with those after curetting in properly selected cases. When we eliminate from our recurrent cases faulty curetting when the bone shell was intact and attempted curetting when the bone shell was destroyed, curetting has to its credit recoveries with perfect function in practically 100 per cent of the cases, and even if x-rays or radium could accomplish the same result in this group with intact bone shell, it would be more costly and take much more time. When the bone shell is destroyed, there is no question that irradiation should be tried first. Irradiation for recurrence after curetting is not so successful as irradiation without operation, nor has irradiation after recurrence following curetting prevented metastasis in the cases reported in the literature, notably the one reported by Ewing and Stone in the ARCHIVES OF SURGERY in 1923, page 289.

The question is, What is the danger of irradiation should the tumor be a chondrosarcoma or myxosarcoma? We have sufficient evidence to indicate that we may expect little or nothing of irradiation of the myxoma, or the chondroma, or the chondrosarcoma. The possibility of these tumors occurring in the epiphysis with x-ray pictures not unlike that of the giant cell tumor makes the problem difficult. In this malignant tumor of the epiphysis, the bone shell is usually partially destroyed. Therefore, from an x-ray standpoint, if the tumor is of the giant cell variety, the first treatment should be irradiation. I am not prepared to make any definite statement, but I am inclined to the view that, in doubtful cases, the nature of the lesion should be positively settled by a biopsy, provided the operator or his pathologist is competent to make a diagnosis. If not, irradiation should be the first method of treatment.

In conclusion, I want to call attention to the original view of the authors that osteitis fibrosa and the giant cell tumor are phases of bone repair; the first a healing reaction, the second an active vascularizing phase. In osteitis fibrosa, the tendency is to spontaneous reossification or healing. In the giant cell tumor this is not the case. Here the process leads to the formation of a mass of vascular tissue, in which giant cells predominate. The authors explain these different results with knowledge drawn from embryologic investigations of a new order.

Osteitis fibrosa and the giant cell tumor are specific lesions of bone and, in my opinion, are fundamental in all pathologic conditions of bone, just as chronic cystic mastitis is fundamental in all pathologic conditions of the breast, and, on the whole, is not unlike these benign lesions of bone in that it is a reaction of the parenchyma to some insult which, apparently, is not necessarily trauma, although trauma seems to be the starting point of osteitis fibrosa and the giant cell tumor. The authors also explain why osteitis fibrosa predominates in the shaft of bones in young persons and the giant cell tumor in the epiphysis of patients of a later decade.

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INTRODUCTION

Since the time of Galen [1] a form of lesion related to osteitis fibrosa and giant cell tumor has been known to medical writers under the term of epulis, a tumor of the alveolar border. But the increased discussion concerning etiology, beginning with Nélaton's [2] contribution to giant cell tumor in 1860, and Virchow's [3] description of a solitary bone cyst in 1876, has failed to furnish a unified conception of the underlying pathologic processes of this group of lesions, despite the constant progress made.

In this paper an attempt is made to show that a single group of pathologic processes concerned in the repair of injured bone is responsible for this group of clinical entities. The classifications, therefore, of osteitis fibrosa, giant cell tumor, epulis of the alveolar border and giant cell tumor in the tendon sheaths of the xanthoma type have been regrouped on the basis of a fundamental relationship established by the observations reported in this article. The material on which this report is based was made available by Dr. Joseph Colt Bloodgood in the Surgical Pathological Laboratory of the Johns Hopkins Hospital, and this group of over 400 cases comprises an accumulation of gross specimens, microscopic sections, x-ray pictures, clinical histories and a system of case follow-ups for which his personal efforts during the past thirty-five years are largely responsible. In addition to the references noted elsewhere, we wish to make special mention of the recent and larger series of cases contributed by Stewart,[4] Simon,[5] Bloodgood,[6] Ewing,[7] Kolodny,[8] Coley,[9] Barrie,[10] Lewis,[11] Codman,[12] Christensen,[13] and

1. Galen, cited by Simon, W. V.: Die Knochensarkome, Ergebn. d. Chir. u. Orthop. **16**:364, 1923.

2. Nélaton, E.: Tumeurs benignes des os, Paris, 1860.

3. Virchow, R.: Ueber die Bildung von Knochencysten, Monatsb. d. kgl. preusz. Akad. d. Wissenschaften zu Berlin, 1876, p. 369.

4. Stewart, M. J.: The Histogenesis of Myeloid Sarcoma, Lancet **2**:1106, 1922.

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12. Codman, E. A.: The Nomenclature Used by the Registry of Bone Sarcoma, Am. J. Roentgenol. **13**:105, 1925.

13. Christensen, F. C.: Bone Tumors, Ann. Surg. **81**:1074, 1925.

MacQuire and McWhorter [14] on giant cell tumor and by Silver,[15] Knaggs,[16] Elmslie,[17] Bloodgood,[18] Morton [19] and Konjetzny [20] on osteitis fibrosa from which valuable corroborative data were obtained.

BONE CYSTS

Clinical Features.—Although the limits of osteitis fibrosa have been widely extended since the time of von Recklinghausen [21] to include a multiplicity of entities, the solitary bone cyst, which is a form of osteitis fibrosa found usually in the shaft of the long bones of young adults, presents certain uniform characteristics which allow this group of lesions to be discussed separately from a pathologic standpoint.

Von Mickulicz [22] was among the first to observe that the age of a patient with a typical bone cyst is usually less than 21. Bloodgood,[18] writing on this subject in 1910, called attention to the fact that the patient was generally less than 18, and Silver,[15] in his review of ninety-seven cases in 1912, found only eighteen cases in which the patients were past the age of 20. In a review of bone cysts, Elmslie,[17] in 1914, found a similar age incidence. In 175 cases of bone cysts in this series, the average age of the patients is between 10 and 15, although in about 20 per cent the patients are more than 21. This age distribution is one of the outstanding clinical features of the disease.

More noteworthy than the age incidence is the location of these tumors, for in the large majority of cases of solitary bone cyst the lesions are confined to three favorite sites, the upper shaft of the femur, the humerus or the tibia. In Silver's [15] table of ninety-seven cases, the tumor was found in the femur in thirty-one cases, in the humerus in twenty-five and in the tibia in fifteen. Elmslie [17] was

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14. MacGuire, C. J., and McWhorter, J. E.: Sarcoma of Bone: An Analysis of Fifty Cases, Arch. Surg. **9**:545, 1924.

15. Silver, D.: The So-Called Benign Cyst of the Bones, Am. J. Orthop. Surg. **9**:563, 1912.

16. Knaggs, R. L.: The Inflammatory and Toxic Diseases of Bone, New York, William Wood & Company, 1926.

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19. Morton, J. J.: The Generalized Type of Osteitis Fibrosa Cystica, Arch. Surg. **4**:534 (May) 1922.

20. Konjetzny, G. E.: Die Sogenannte "Lokalisierte Osteitis fibrosa," Arch. f. klin. Chir. **121**:567, 1922.

21. Von Recklinghausen: Die Fibrose oder deformierende Osteitis die Osteomalacie und die osteoplastiche Carcinose, Festschr. zu Rudolf Virchow, 1891.

22. Von Mickulicz: Discussion of case of Hans Haberer, Centralbl. f. Chir. **31**:1323, 1904.

TABLE 1.—*Typical Bone Cysts*

Path. No.	Race, Sex, Age	Location*	Symptoms†	X-Ray	Treatment	Microscopic	Results
39960	W F. 18	Humerus, shaft	Fracture	Cystic, expanded	.....	.....	.....
39258	W. M. 60	Tibia, upper	Fracture, 4 years	Expanded, perforated	Amputation advised	.....	.....
39098	W. M. 10	Humerus, shaft	.....	.....	Curetted	Typical osteitis fibrosa	.....
38104	W. M. 8	Humerus, upper	Tumor, 1 month	Cystic, expanded	.....	.....	.....
38074	W. M. 36	Femur, neck	Limp, 6 months	Cystic, deformity	Explored	.....	.....
37796	W. M. 2	Humerus, shaft	Fracture, 4 years	Cystic, deformity	Amputation	Osteitis fibrosa, bone formation	.....
37624	W. F. 21	Femur, lower	Fracture, limp, 8 wks.	Cystic, encapsulated	.....	.....	.....
37618	W. F. 7	Tibia, upper	Tumor	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 3 years
37488	W. M. 16	Humerus, upper	Fracture, 2 weeks	Cystic, encapsulated	.....	.....	.....
37146	W. F. 9	Radius, shaft	Fracture, pain, 3 mos.	Cystic, expanded	.....	.....	Healing 2½ years
37114	W. M. 14	Femur, upper	Limp	Cystic, encapsulated	.....	.....	.....
37062	W. F. 45	Radius, lower	Fracture, tumor, 2 yrs.	Ossifying cyst	.....	.....	.....
36932	W. F. 22	Tibia, lower	Trauma	Ossifying cyst	.....	.....	.....
36814	W. F. 21	Humerus, upper	Pain, 6 months	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 6 months
36850	W. M. 15	Humerus, lower	Fracture, 5 years	Huge ossifying cyst	.....	.....	.....
36726	W. M. 4	Humerus, upper	Fracture, 6 weeks	Cystic, encapsulated	Osteotomy	No tissue removed	.....
36718	W. M. 17	Humerus, upper	Fracture, pain, 7 yrs.	Cystic, expanded	.....	.....	.....
36662	W. M. 9	Femur, upper	Fracture, tumor, 6 mos.	Cystic, encapsulated	.....	.....	.....
36611	C. F. 4	Humerus, upper	Trauma, 1 week	Cystic, encapsulated	Incised	Typical osteitis fibrosa	.....
36580	W. M. 15	Fibula, lower	.....	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	.....
36518	W. F. 40	Femur, upper	Fracture	Cystic, expanded	Operation advised	.....	.....
36516	W. M. 10	Humerus, upper	Fracture	Cystic, expansion	Curetted	.....	Recurred
36374	W. F. 36	Femur, lower	Tumor, 1 year	Cystic, expanded	Curetted	Typical osteitis fibrosa	.....
36268	W. M. 9	Humerus, shaft	Trauma, 1 year	Expansion, fracture	Osteotomy, crushing	Typical osteitis fibrosa	Well 2 years
36260	W. M. 7	Humerus, upper	Trauma, 1 year	Cystic, encapsulated	.....	.....	.....
36140	W. F. 12	Femur, upper	Trauma	Cystic, expanded	.....	.....	.....
36000	W. F. 32	Femur, lower	Tumor, 10 months	Cystic, expanded	Incised	Typical osteitis fibrosa	.....
35884	W. M. 5	Femur, upper	Trauma, 2 months	Cystic, expanded	.....	.....	.....
35134	W. 6	Tibia, upper	.....	Cystic, expansion	.....	.....	.....
35066	W. M.	Tibia, upper	Trauma, 3 months	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 4 years
35006	W. 21	Femur, upper	Fracture, trauma, 5 months	Expanded cyst	Incised	Typical osteitis fibrosa	Well 1 year
34452	W. F. 30	Tibia, lower	Pain, 18 months	Cystic	Incised	Typical osteitis fibrosa	.....
34314	W. F. 25	Femur, neck	Trauma, 3 years	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	.....
33804	W. M. 9	Tibia, shaft	Tumor, 16 months	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 19 months
33326	C. M. 6	Humerus, upper	Trauma, 7 months	Cystic, expanded	.....	.....	.....
33006	W. M. 31	Femur, upper	Limp, 15 months	Cystic, expanded	.....	.....	Well 1 year

32732	W. F. 5	Tibia, upper	Tumor, 3 years	Ossifying cyst	Incised	Typical osteitis fibrosa	Well 3 years
32415	W. M. 22	Humerus, shaft	Pain, 4 years	Cystic, expansion	.....	.....	.....
32336	W. F. 14	Tibia, lower	Trauma, 2 weeks	Ossifying cyst	.....	.....	Well 1 year
32199	W. M. 13	Femur, upper	Tumor, 1 year 9 mos.	Cystic, expansion	Operation advised	.....	.....
32153	W. M. 45	Humerus, upper	Trauma, 38 years	Cystic, encapsulated	.....	.....	.....
32120	W. M. 11	Humerus, upper	.....	Cystic, expansion	.....	.....	Well 2 years
32128	W. M. 11	Humerus, upper	Trauma, 1 year	Cystic, encapsulated	Incised	Typical osteitis fibrosa	.....
32094	W. M. 10	Humerus, upper	Trauma, 10 days	Cystic, encapsulated	Curetted	.....	.....
31944	W. M. 17	Clavicle, sternal end	Tumor, 6 months	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 5 years
31854	W. M. 12	Humerus, shaft	Fracture, 6 years	Cystic, bending	.....	.....	Well 6 months
31820	W. F. 36	Ulna, upper shaft	Trauma	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 3 years
31419	W. M. 50	Tibia, lower	Tumor, 25 years	Cystic, expansion	Curetted	Typical osteitis fibrosa	.....
31414	W. M. 10	Humerus, upper	Fracture, 1 year	Cystic, expansion	.....	.....	.....
31163	W. F. 33	Femur, upper	Trauma, 28 years	Expanded cyst	.....	.....	.....
30840	W. M.	Femur, neck, shaft	Fracture	No note	No note	Typical osteitis fibrosa	Well 7 years
30782	W. M. 8	Humerus, upper	Fracture, trauma	Ossifying cyst	.....	.....	.....
30359	W. M. 50	Femur, upper	Pain, 20 years	Ossifying cyst	.....	.....	.....
29746	W. M. 24	Fibula, lower	Tumor, 16 years	Cystic, bending	.....	.....	.....
29644	W. M. 49	Fibula	Tumor, 25 years	Cystic, encapsulated	.....	.....	.....
29108	W. F. 10	Femur, upper	Trauma	Large cyst	.....	.....	.....
28963	W. F. 45	Femur, shaft	Fracture, 8 years	Cystic, bending	.....	.....	.....
28913	W. F. 23	Femur, trochanter	Pain, 3 years	Fracture through cyst	Curetted	Typical osteitis fibrosa	Well 7 years
28743	W. F. 13	Femur, upper	Tumor, 6 years	Cystic, encapsulated	.....	.....	.....
28485	W. M. 12	Tibia, shaft	Fracture, 5 years	Cystic, encapsulated	Excision	Typical osteitis fibrosa	Well 7 years
28393	W. M. 10	Humerus, upper	Trauma, 18 months	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 3 years
28160	W. F. 49	Clavicle, end	Tumor, 6 months	Cystic, expansion	.....	.....	.....
28056	W. F. 7	Humerus, upper	Trauma, 7 months	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 2 years
28055	W. M. 4	Femur, upper	Trauma, 3 weeks	Cystic, expansion	.....	.....	Well 1 year
28054	W. F. 8	Humerus, upper	Trauma	Ossifying cyst	.....	.....	Well 1 year
27889	W. 11	Femur, upper	Trauma, 1 year	Cystic, expansion	Amputated	Typical osteitis fibrosa	Well 7 years
27792	W. M. 16	Humerus, upper	Trauma, 5 days	Fracture, perforation	Curetted	Typical osteitis fibrosa	Well 2 years
27703	W. M. 22	Femur, shaft	Fracture, 2 years	Cystic, expansion	Explored	Typical osteitis fibrosa	Well 2 years
27375	W. F. 40	Tibia, shaft	Trauma as child	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 2 years
27324	W. M. 10	Humerus, upper	Trauma, 8 days	Cystic, expansion	.....	.....	Well 2 years
27057	W. M. 33	Femur, lower	Pain, 3 months	Healing bone	Curetted	Typical osteitis fibrosa	Well 7 years
26918	W. M. 10	Tibia, shaft	Tumor, 1 year	Cystic, expansion	Resected	Typical osteitis fibrosa	Well 8 years
26620	W. F. 7	Clavicle, end	Tumor, 8 months	Cystic, expansion	.....	.....	Well 3 years
26312	W. M. 15	Humerus, upper	Fracture, 3 weeks	Ossifying cyst	Curetted	Typical osteitis fibrosa	Well 6 years
26143	W. F. 4	Humerus, upper	Fracture	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 2 years
26311	W. 10	Femur, upper	Fracture	Cystic, expansion	Resected	Typical osteitis fibrosa	Well 3 years
25656	W. M. 15	Humerus, shaft	Fracture, 1 week	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 7 years

* "Upper" and "lower" indicate metaphyseal regions.

† In this and subsequent tables the symptom given is the symptom at time of onset.

TABLE 1.—*Typical Bone Cysts—Continued*

Path. No.	Race, Sex, Age	Location	Symptoms	X-Ray	Treatment	Microscopic	Results
25542	W. F. 17	Tibia	Tumor, 12 years	Cystic, bending	Resection	Typical osteitis fibrosa	.....
25345	W. M. 17	Humerus, upper	Fracture	Encapsulated cyst	.....	.....	Well 3 years
25109	W. F. 2	Tibia, lower third	Deformity, fracture	Fracture, rarefaction	Excision	Typical osteitis fibrosa	Well 9 years
24915	W. M. 4	Femur, upper	Fracture	Cyst with fracture	.....	.....	Well 3 years
24746	W. F. 15	Femur, lower	Trauma, 8 years	Cystic, expansion	Excision	Typical osteitis fibrosa	Well 3 years
24096	W. F. 24	Tibia, shaft	Tumor, 10 years	Expansion, encapsulation	Excision	Typical osteitis fibrosa	Well 3 years
24009	W. M. 5	Femur, upper	Trauma, 20 months	Cystic, expansion	.....	.....	Well 1 year
23617	W. M. 12	Femur, upper	Fracture	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 3 years
21191	W. M. 26	Radius, lower	Tumor, 10 years	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 10 years
20296	W. F. 26	Tibia, lower	Tumor, 5 years	Cystic, expansion	Excision	Typical osteitis fibrosa	Well 4 years
20209	W. F. 18	Femur, upper	Tumor	.....	Incised	Typical osteitis fibrosa	Well 5 years
20646	C. M. 35	Femur, shaft	Tumor, 5 years	Cystic, expansion	Amputated	Typical osteitis fibrosa	Well 7 years
19587	W. M. 8	Tibia, upper	Tumor	Cystic, expansion	Curetted	Typical osteitis fibrosa	Well 4 years
17433	W. F. 12	Radius, lower	Tumor	Cyst with fracture	.....	.....	.....
16454	W. F. 5	Tibia, lower	Tumor, 2 years	Encapsulated cyst	Curetted	Typical osteitis fibrosa	.....
16032	W. M. 20	Femur, lower	Fracture, 8 years	Encapsulated cyst	.....	.....	Well 3 years
15398	W. F. 3½	Tibia, lower	Tumor, 1 year	Healing cyst	Explored	Typical osteitis fibrosa	Well 8 years
14131	W. M. 16	Humerus, shaft	Pain, 1 month	Expansion, fracture	Curetted	Typical osteitis fibrosa	Well 7 years
13831	W. M. 16	Tibia, shaft	Trauma, 3 years	Expansion, encapsulated	Explored	Typical osteitis fibrosa	Well 7 years
13829	W. F. 7	Femur, upper	Limp, 7 months	Encapsulated cyst	Excision	Typical osteitis fibrosa	Well 8 years
13593	W. F. 9	Humerus, shaft	Trauma, 8 days	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 16 years
13329	W. F. 8	Humerus, upper	Fracture, 10 days	Healing cyst	Excised	Typical osteitis fibrosa	Well 16 years
12231	W. M. 6	Humerus, upper	Fracture	Cystic, encapsulated	Curetted	Typical osteitis fibrosa	Well 9 years
10524	W. M. 5	Femur, upper	Tumor	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 4 years
10474	C. M. 18	Humerus, upper	Pain, 3 weeks	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 10 years
10275	W. F. 3½	Humerus, upper	Trauma, 2 years	Fracture through cyst	Curetted	Typical osteitis fibrosa	Well 12 years
9732	W. M. 18	Humerus	Fracture	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 13 years
9718	W. F. 40	Fibula, lower	Tumor, 24 years	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 2 years
9566	W. F. 21	Femur, lower	Trauma, 6 months	Encapsulated cyst	Amputated	Typical osteitis fibrosa	Well 10 years
9155	W. M. 13	Humerus	Tumor, 2 years	Encapsulated cyst	Curetted	Typical osteitis fibrosa	Well 2 years
9025	W. F. 6	Ulna	Tumor, 7 months	Cystic, expansion	.....	.....	Well 16 years
8324	W. F. 21	Femur, lower	Tumor, 10 years	No note	Amputated	Typical osteitis fibrosa	Well 20 years
6891	W. F. 11	Tibia, upper	Tumor, 1 year	Cystic, expansion	Curetted	Typical osteitis fibrosa	.....
5533	C. F. 38	Femur, lower	Tumor, 5 years	No note	Resected	Typical osteitis fibrosa	Died of hemorrhage
5358	W. F. 7	Femur, upper	Trauma, 4 months	Cystic, expansion	Resected	Typical osteitis fibrosa	Well 20 years
4993½	W. M. 8	Humerus, upper	Fracture	Cystic, expansion	.....	.....	.....
3903	W. F. 7	Humerus, upper	Fracture, 1 year	Cystic, expansion	Incised	Typical osteitis fibrosa	Well 17 years

impressed with the fact that the upper part of the femur and the upper part of the humerus were the prevalent locations for this type of lesion. The figures in our series are in accord with the observations of these authors. In 135 cases of solitary bone cysts, fifty-two were in the femur, forty-five in the humerus and thirty in the tibia. The fibula is next in frequency with eight lesions. In the cases in which the cyst was in the femur, thirty-two of fifty-two were present in the upper end, most of these being in the region of the greater trochanter. In the humerus, lesions in the upper end of the bone predominate, thirty-six of the forty-five cases in our series being in that locality, while in the tibia there is a similar predilection to involvement of the upper end. In all, about 75 per cent of these lesions showed a metaphyseal location in these three bones.

At the age and in the locality in which these tumors occur there is a relationship to an unossified epiphyseal line. The bone involved is therefore typically an area of new bone in a metaphyseal region. This fact would appear to relate the pathologic process involved to new bone formation, and in the microscopic study of these lesions, an attempt will be made to trace this relationship.

It is important to point out here that while the majority of bone cysts show this metaphyseal location, there is a fair percentage of them (16 per cent) which are found toward the region of the midshaft. This variation in site is explicable by the duration of the clinical symptoms. As will be seen from table 1, the average duration of symptoms is two and one-half years. In one fifth of the cases, the duration averaged ten years, and in several cases the patients had symptoms dating back from twenty to forty years. This long latent period preceding the diagnosis of the disease allows ample time for the affected area to progress gradually toward the region of the midshaft as the bone grows. In extreme cases in which from ten to forty years have elapsed, the reason for the occurrence of the bone cysts in patients more than 20 years of age is evident. Here the lesion takes the form of the so-called latent bone cyst discovered late in life as the consequence of some clinical incident leading to a roentgen examination, the previous presence of the tumor remaining unsuspected because of the absence of symptoms.

In accordance with this, a review of the histories shows that pain plays a mild rôle as a symptom of onset and that trauma with pathologic fracture or swelling is a more frequent cause in bringing the patient to the physician, pathologic fracture occurring in 45 per cent of the cases. In all cases we are impressed with the mildness of the clinical features, for only rarely is there extreme pain or marked bending deformity. The same facts are borne out by the clinical course which although protracted in many cases, is always benign, no patient ever dying from the direct cause of the disease.

X-Ray Features.—The typical x-ray picture of a bone cyst emphasizes many of the clinical features, the ununited epiphysis near the diseased area indicating the youthful age of the patient and the metaphyseal location of the lesions (fig. 1 *A, B* and *C*). A central area of bone destruction, which occurs most frequently in the upper part of the femur, humerus or tibia, casts little or no shadow in the roentgenogram and is crossed here and there by one or more trabeculations. About this area the cortex is thin and expanded to form a symmetrical and fusiform swelling. Often the bone is fractured at this site and along the margins of the fracture new bone formation casts a dense

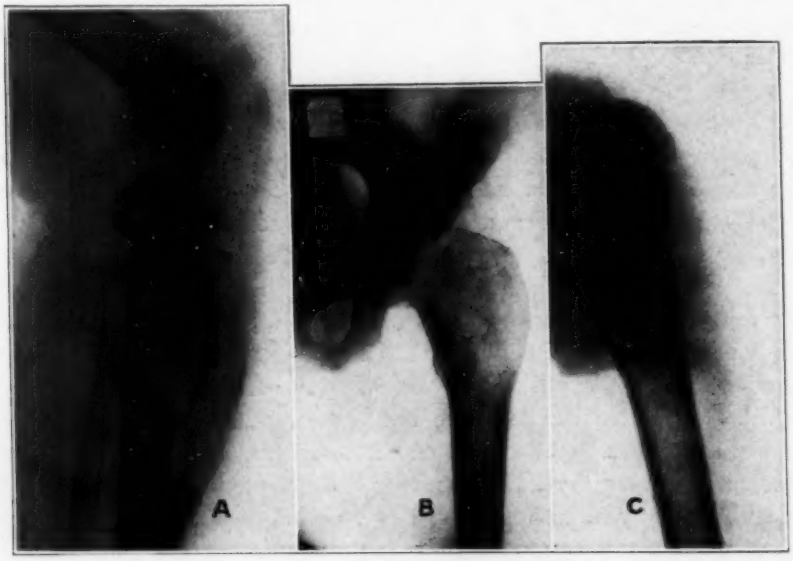

Fig. 1 (nos. 35253, 34174 and 37796).—X-ray pictures of typical bone cysts in the localities most frequently affected: *A*, upper part of tibia; *B*, upper part of femur, and *C*, upper part of humerus. The lesions are near or at the metaphysis, and the ununited epiphysis in *A* and *C* indicate the youth of the patients. A pathologic fracture is shown in the upper part of the humerus.

shadow. These fractures tend to heal, and with healing the lesions frequently will ossify and disappear. When the diseased area persists for any length of time, however, the condition progresses toward the region of the midshaft.

The shell of bone about the affected portion is rarely perforated except by fracture. Often this portion of the bone is bowed or thickened. The new bone formation is then subperiosteal and cortical and produces no periosteal spicules, either parallel or radiating.

Gross Appearance.—The bone overlying the cyst varies in thickness according to the duration of the symptoms, the thicker shell encountered

in old cases indicating that a healing reaction is taking place (fig. 2). A connective tissue lining is usually beneath the bone shell, and further toward the interior is the cavity which most frequently contains a serous fluid.

Bloodgood [18] has ably given a classification of the variations in the gross pathologic changes in these cavities or cysts. They may or may not have a connective tissue lining, and fluid or solid fibrous tissue may be found beneath. Calcium spicules like snow may be found on the inner side of the lining, or the remains of tissue resembling the grumous giant cell tumor may be disclosed.

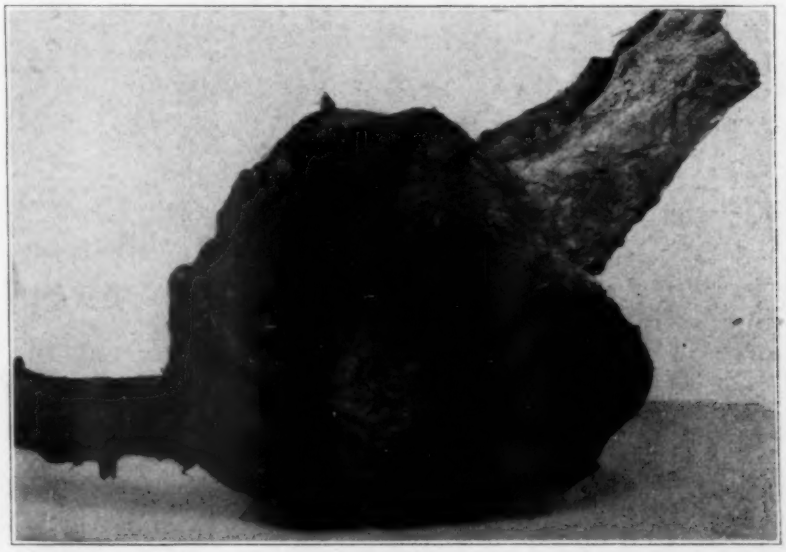

Fig. 2 (no. 8324).—Gross specimen of a large bone cyst of ten and one-half years' duration in the lower end of the femur in a woman, aged 21. There is an unusually large amount of fibrous tissue and new bone formation in the cyst wall because of the age of the lesion.

In any event the contents of the cavity explored in the gross give little or no clue to an area of new cartilaginous bone such as the clinical features of age incidence and location would lead one to expect. In the shell of bone overlying the cavity, there is frequently a thickness and firmness extending into the fibrous lining which suggests the formation of new bone, but the location indicates that this is proceeding from the cortical region of the shaft rather than from a central metaphyseal location. Aside from this cortical reaction the gross specimens suggest a process of bone destruction rather than one of new bone formation.

Microscopic Analysis.—A microscopic analysis of the bone cyst, although adding much to our information concerning the pathologic

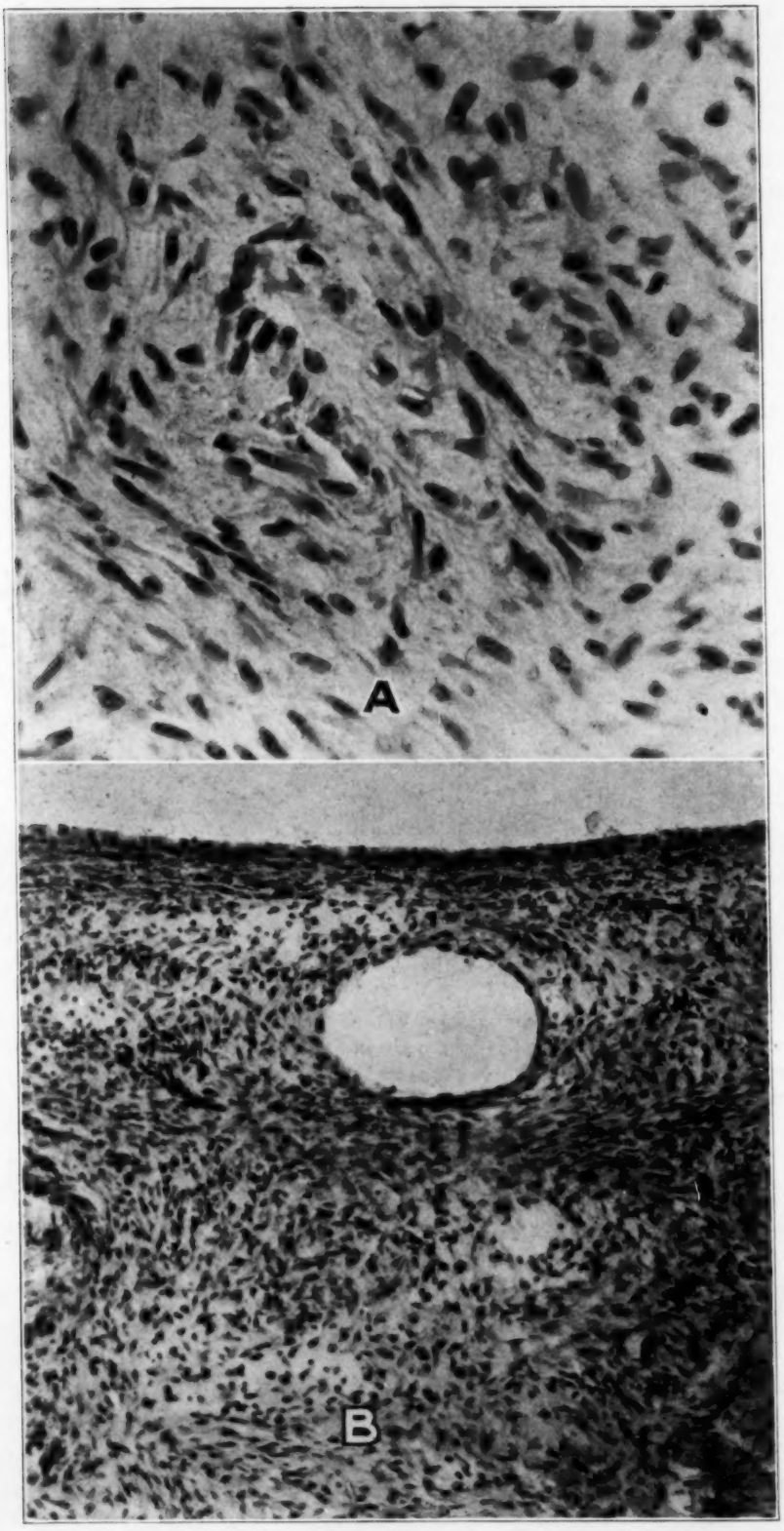

Fig. 3 (nos. 40124 and 24746).—Two typical areas of osteitis fibrosa. In figure *A* the intercellular substance is emphasized. In figure *B* there is condensation of fibrous tissue in the wall of the large cyst. A small cyst also is shown.

changes, fails to disclose in most instances a bone destructive process which would explain the cavity formation. Most of the tissue composing the cyst wall is fairly uniform and consists of spindle cells and fibroblasts among which there is much clear intercellular substance (fig. 3 *A*).

The tissue varies in relation to special areas. These special areas are of three main types: (1) cysts with or without old hemorrhage, (2) bone islands or bone trabeculae and (3) vessels in areas of fresh hemorrhage. Attention is first directed to the cyst wall. About the cyst wall there is a condensation of connective tissue to form a fibrous lining (fig. 3 *B*). Behind this lining layer embryonic fibroblasts are lay-

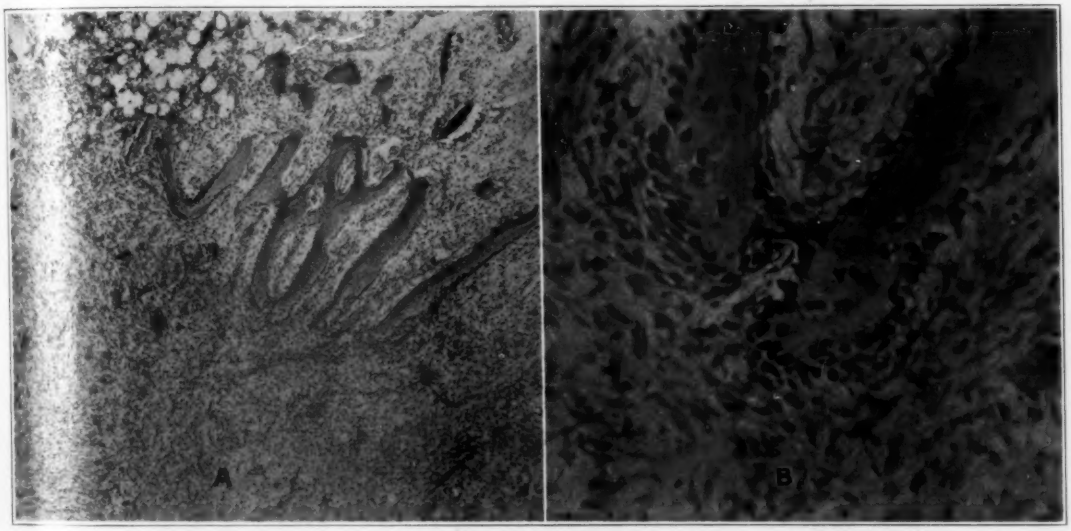

Fig. 4 (no. 19179).—*A* low and *B* high power of new bone formation in osteitis fibrosa. Osteoblasts derived from fibroblasts are laying down osteoid tissue. These spicules of new bone are characteristic of the process termed fibro-ostosis in this paper.

ing down intercellular substance, with the formation of osteoblasts and the direct proliferation of new bone. Occasionally, along the cyst wall or where two cysts walls meet with rupture in the wall, giant cell areas with round cells will be seen. Within the smaller cysts the remains of old hemorrhages are often found. In the larger cysts this is less likely to occur.

In regard to the substance around the bone spicules, the first or proximal row of cells is an actively proliferating layer of osteoblasts and numerous gradations between these cells and the fibroblasts (fig. 4 *A* and *B*). Beyond there is generally a loose fibrous tissue, almost myxomatous in appearance. Apparently, the process is from

spindle cell to fibroblast to osteoblast and then to bone formation, the bone at first being osteoid tissue previous to calcification.

Areas of fresh hemorrhage or new blood vessels present interesting features. Frequently an area with fresh blood will have a mixture of round and spindle cells in the neighborhood, or proximal to a new vessel will be seen a sprinkling of large giant cells of the epulis type (fig. 5). This relation of round cells and giant cells to spaces of red blood cells is most significant, and while some pathologists feel that giant cells are called on to absorb these hemorrhagic deposits (Konjetzny [20]), it is important to emphasize that the giant cells are associated only with new vessels

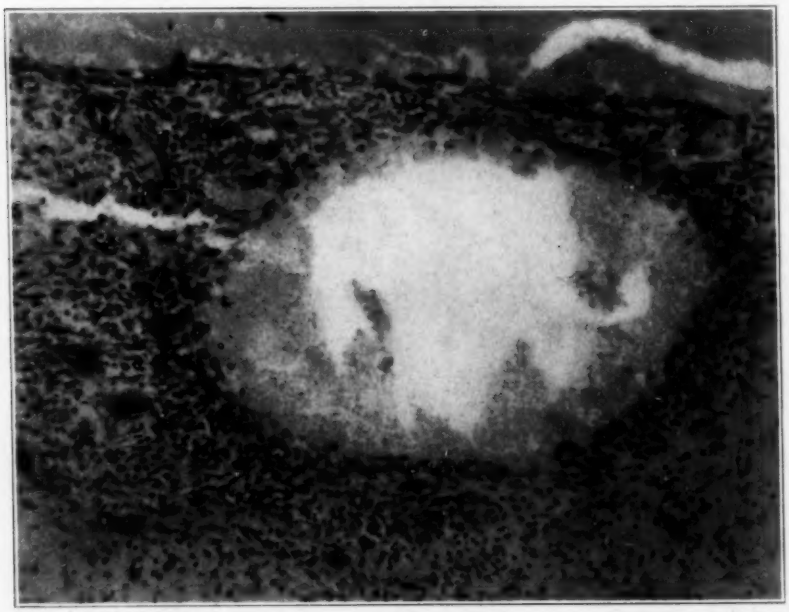

Fig. 5 (no. 28609).—Photomicrograph from a bone cyst showing a newly formed cyst containing red blood cells and surrounded by a sprinkling of giant cells.

and fresh hemorrhages rather than with the old blood seen within the cysts. For this reason it is more probable that the order of pathologic events so far as microscopic analysis can disclose them is: (1) the formation of giant cell areas followed by new blood vessels and hemorrhage; (2) the absorption of hemorrhage with cyst formation, and (3) the lining of the cyst by fibrous tissue which is gradually transformed into bone. In any event the three processes of hemorrhage, cyst formation and new bone construction which represent the special areas in osteitis fibrosa seem to be related and to have a definite influence on the character of the adjacent stroma.

Minute areas of calcification are often seen in the new bone laid down in osteitis fibrosa. Bone via the cartilaginous route as seen in osteogenic sarcoma, however, has not been observed, neither has true myxomatous tissue. Although much has been spoken about myxomatous degeneration in osteitis fibrosa, the interpretation placed on such areas here is that they are loose embryonic connective tissue.[22a]

Nature of Osteitis Fibrosa.—The foregoing analysis of the histology of the cyst wall in osteitis fibrosa leads to the conclusion that the process involved is essentially one of fibrous proliferation and new bone formation and therefore a repair or healing process. We do not see in this tissue evidence of an inflammatory reaction, although repair in bone following a medullary abscess may show the same healing phase typical of osteitis fibrosa.

In keeping with this view of the nature of osteitis fibrosa tissue, is the experimental work of Macewen [23] in his studies on the growth of bone. He found as we do in sections taken from numerous areas in the bone, that regeneration takes place independently of the periosteum. The patients suffering from the lesions considered here are in the younger period of life when (as Macewen has pointed out) the proliferating power of the bone cell is at its height. The bone involved by the disease reacts vigorously, and we find bone formation taking place through the activity of osteoblasts in a medium of fibrous tissue, without the transitory stage of cartilaginous calcification. The photomicrographs illustrated in this article, and indeed most illustrations of osteitis fibrosa, show an exact duplicate of the process depicted in Macewen's [23] book on new bone produced experimentally, growing inside of glass tubes.

The conclusion that areas of osteitis fibrosa represent a healing reaction in bone, attacks seriously the claim of osteitis fibrosa to consideration as a pathologic entity. In accordance with this view are the records of the grading files made during this study. Here diagnosis in the osteitis fibrosa group showed the largest percentage of error. Abscess walls, bits of capsule from central sarcoma of bone, or secondary metastatic tumor, and periosteum overlying ossifying hematoma or exostosis were all inadvertently placed among the sections classed as typical osteitis fibrosa. From a standpoint of microscopic diagnosis, it was a veritable dumping ground. The reasons for this are to be found in the nonspecific nature of the tissue reaction, erroneously termed osteitis fibrosa. It is not an inflammation in fibrous tissue or in bone but a process of

22a. This loose embryonic connective tissue as pointed out by Lériche and Policard (Physiology of Bone, St. Louis, C. V. Mosby, 1928) is a pre-osseous edema pervading the connective tissue, and is always the first step in bone formation in this tissue.

23. Macewen, W.: The Growth of Bone, Glasgow, James Macelhose and Sons, 1912, figs. 27 and 28.

repair constituting a natural defensive reaction of cancellous bone, cortical bone and periosteum against pathologic invasion, whether the invading lesion is an abscess, a sarcoma or a giant cell tumor (figs. 6 *A* and *B* and 7).

In most cases of osteitis fibrosa this healing reaction is found around an evacuated area of bone destruction. The solitary bone cyst under

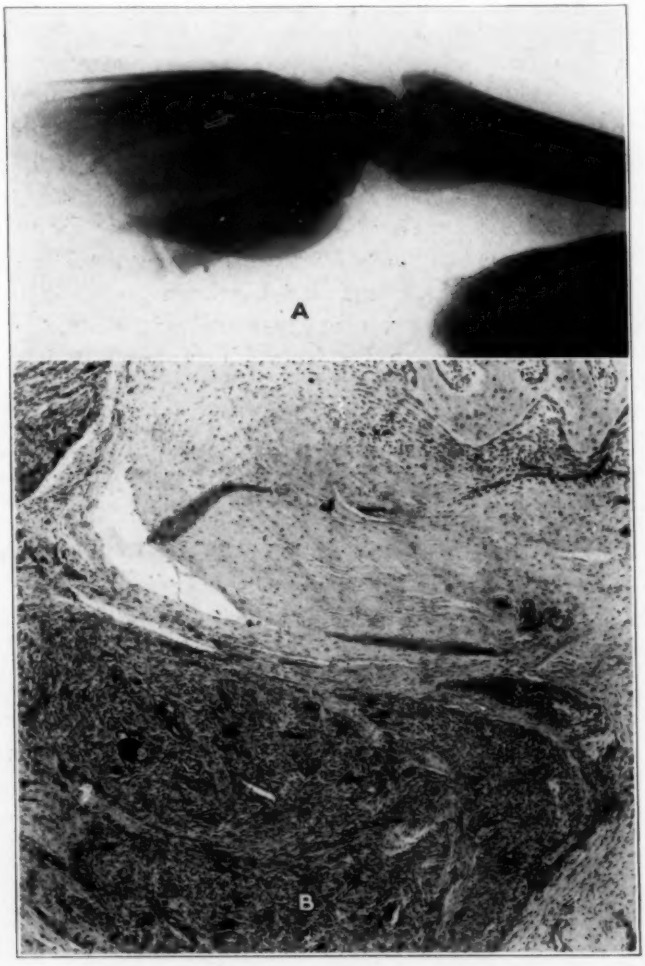

Fig. 6 (no. 36614).—Bone cyst formed about a foreign body. *A* is an x-ray picture and *B* is a photomicrograph from the same case. The patient was struck by a piece of flying steel eighteen months previously, the steel entering the hand. The superficial wound healed. Fourteen months later, swelling and pain occurred at the site of injury. The x-ray picture shows the cyst about the foreign body. The photomicrograph shows fibro-ostosis (new bone and fibrous tissue) surrounding an area of granulation tissue.

discussion shows such an area of bone destruction in the form of an enclosed cavity, and about it is the typical healing reaction which we believe is best termed fibro-ostosis (indicating new bone formed directly from fibroblasts). The reparative nature of this reaction of fibro-osteosis is evidenced clinically by the benign course of the disease and the tendency of the lesions to undergo spontaneous healing. Clinically and pathologically too, it would seem that the bone destructive process soon becomes arrested or often progresses without noteworthy symp-

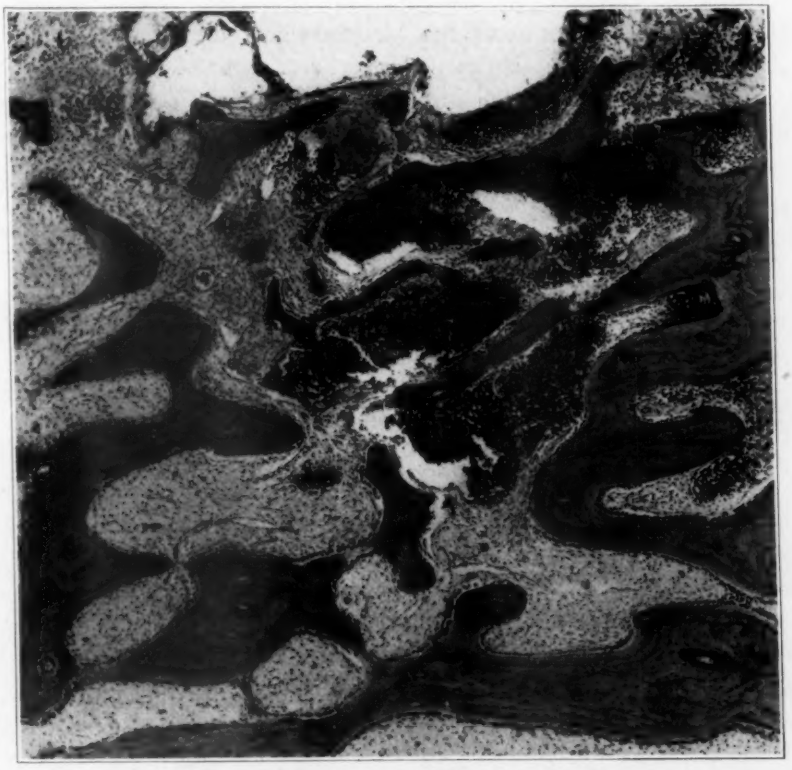

Fig. 7 (no. 15745 [Bone Tumors: Group 9]).—Section taken from the margin of a Ewing's sarcoma of bone. The undestroyed bone is reacting to form a protective wall about the tumor, laying down new bone surrounded by osteoblasts. These new bone spicules with the surrounding fibrous tissue resemble osteitis fibrosa. A nest of round sarcoma cells is seen in the upper portion of the picture.

toms, for when we recognize the condition clinically and make the diagnosis or explore, the bone destructive phase is practically always complete and nothing is encountered but the healing phase. This fibroid process of repair sometimes extends over a period as long as forty-five years, and then a latent bone cyst is recognized. The persistence of the cyst beneath this healing reaction is due to nature's difficulty in collapsing

a cavity with rigid walls, and when fracture or a crushing procedure at operation aids in collapsing this cavity, the lesion heals.

HISTOLOGIC VARIANTS OF THE BONE CYST

The question arises as to what is the original bone destructive process in the bone cyst. In the average case the lesion is of two and one-half years' duration when first observed, and at the end of such a period the condition responsible for the area of bone destruction has disappeared. When bone cysts are grouped according to the duration of symptoms, however, and when the group in which the symptoms average six months are examined, we are able to discover by microscopic examination the nature of the process which forms this cavity in the bone. This group of early cases shows in the x-ray picture a metaphyseal location and a polycystic structure. Twenty-nine in the series of one hundred and seventy-five cases of bone cysts were in this group. Microscopically, they were all classed as giant cell variants of osteitis fibrosa. By this is meant that areas of large multinucleated giant cells embedded in a stroma of round cells, a tissue typical of a giant cell tumor, were always found in early cases of bone cysts examined pathologically. This confirms our microscopic analysis of the typical bone cyst, for as pointed out in the foregoing, there were histologic grounds for assuming that the giant cell areas preceded those of osteitis fibrosa.

In other words, we are inclined to the belief that the bone destructive phase of osteitis fibrosa is characterized by typical tissue of a giant cell tumor. More broadly stated, the average solitary bone cyst in the long bones is a healed or healing giant cell tumor. Not only do twenty-nine early cases of 175 cases of osteitis fibrosa show marked giant cell areas, but sixty cases of giant cell tumor of a series of 226 cases show a healing change toward osteitis fibrosa, most marked at the margins of the tumor but also infiltrating toward the center.

This does not mean that all bone cysts are healed giant cell tumors, nor is it true that giant cell tumors will all progress toward a healed state of osteitis fibrosa. In bone cysts 2 per cent of the cases can be shown to have a bone destructive phase due to a foreign body (fig. 6) or an abscess, and in about 20 per cent of the cases rather loosely classed as osteitis fibrosa some primary disease such as osteomalacia, Paget's osteitis deformans, fragilitis ossium, or osteo-arthritis is responsible for this cyst formation. The majority of solitary bone cysts (78 per cent), however, show their relationship to a preceding giant cell tumor phase (1) by the persistence of giant cell areas most frequent in the younger cysts with a shorter duration of symptoms, and (2) by the fact that these lesions are on the metaphyseal side of the epiphyseal line, bordering on the epiphysis in which giant cell tumors occur.

The polycystic group of osteitis fibrosa also emphasizes the relation of the bone cyst to giant cell tumor tissue, for in these lesions the small young cysts can be seen arising in giant cell areas and fusing together to form the larger cavities.

Detailed consideration of the lesions grouped under the variants of osteitis fibrosa in the metaphyseal ends of the long bones (table 2) and under the classification of polycystic osteitis fibrosa (table 3) brings out more forcibly the basis on which these conclusions rest.

Giant Cell Variants of the Bone Cyst in the Metaphyseal Ends of the Long Bones.—Clinically, these lesions are of shorter duration than

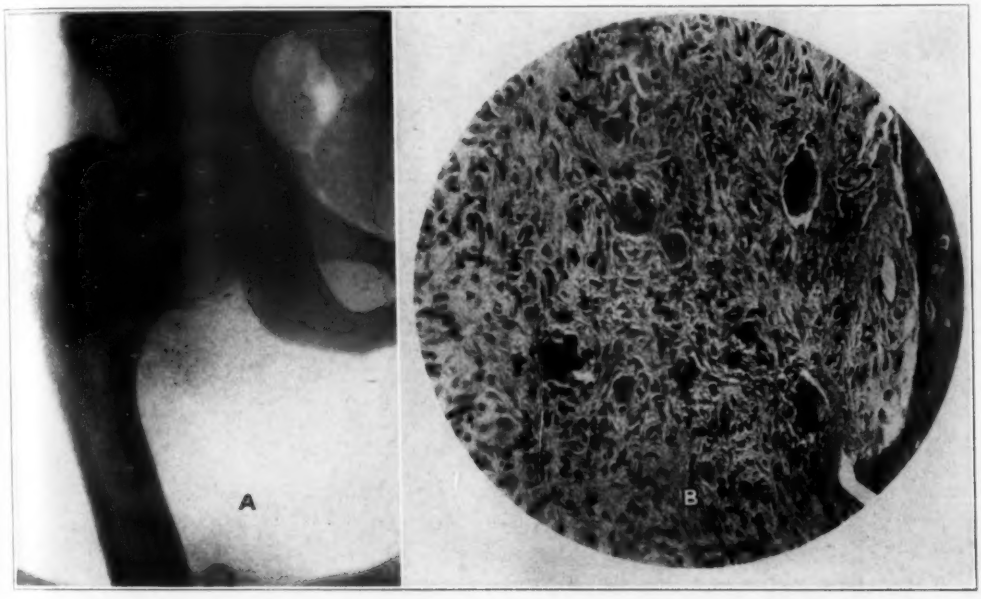

Fig. 8 (no. 17121).—Giant cell variant of osteitis fibrosa near an epiphysis. The x-ray picture, *A*, shows a lesion in the region of the greater trochanter which is inclined to be polycystic. There has been a pathologic fracture. The photomicrograph, *B*, from the same case shows numerous giant cells embedded in the stroma of osteitis fibrosa.

the typical bone cyst. The average duration in the group of cases tabulated in table 2 (with two exceptions) is six months. None of these lesions is found in the region of the midshaft, their location being invariably on the shaft side of the epiphyseal line, close to the area in which typical giant cell tumors occur. A favorite site for these hybrid bone cysts is the region of the greater trochanter in the femur, in which the condition occurred in six of the sixteen cases listed in the series (fig. 8 *A* and *B*). Here it will be recalled there is a separate epiphyseal line in youthful patients, which would seem to indicate that the trans-

TABLE 2.—*Variants of Osteitis Fibrosa in the Metaphyseal Ends of Long Bones* *

Path. No.	Race, Sex, Age	Location	Symptoms	X-Ray	Treatment	Microscopic	Results
40236	W. M. 10	Femur, lower	Trauma, 20 months	Shell perforated	Curetted	Giant cell areas in osteitis fibrosa	Discharged, well
35508	W. M. 15	Femur, condyles	.....	.....	Curetted	Giant cell areas in osteitis fibrosa	Discharged, well
35253	W. F. 5	Tibia, upper	Trauma, 10 weeks	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Discharged, well
34490	W. F. 7	Tibia, upper	Trauma, 4 months	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 1 year
34176	W. F. 14	Femur, trochanter	Pain, 1 year	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 4 years
33882	W. M. 6	Femur, trochanter	Pain, 4 months	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 5 years
32392	W. F. 27	Femur, trochanter	Trauma, 13 years	Polycystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 3 years
32013	W. M. 12	Femur, lower	Pain, 3 months	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 5 years
19179	W. F. 31	Femur, lower	Trauma, 5 months	Cystic, fracture	Amputated	Giant cell areas in osteitis fibrosa	Well 12 years
18871	W. F. 23	Femur, trochanter	Pain, 6 years	Cystic, fracture	Curetted	Giant cell areas in osteitis fibrosa	Well 11 years
17121	W. M. 18	Femur, trochanter	Fracture	Polycystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 9 years
16297	W. F. 13	Tibia, upper	Trauma, 7 months	Cystic, expansion	Curetted	Giant cell areas in osteitis fibrosa	Well 14 years
15893	W. M. 5	Femur, upper	Trauma, 7 months	Cystic, fracture	Curetted	Giant cell areas in osteitis fibrosa	Well 5 years
10693	W. F. 19	Fibula, lower	Tumor, 11 months	Cystic, expansion	Resection	Giant cell areas in osteitis fibrosa	Well 16 years
10352	W. M. 12	Humerus, upper	Trauma, 2 years	Cystic, fracture	Curetted	Giant cell areas in osteitis fibrosa	Well 5 years
5644	W. M. 18	Humerus, lower	Pain, 2 months	Shell perforated	Excised	Giant cell areas in osteitis fibrosa	Well 24 years

* Lesions similar to those in this table but with marked polycystic structure are shown in table 3.

TABLE 3.—*Polycystic Lesions*

Path. No.	Race, Sex, Age	Location	Symptoms	Metaphyseal Location Treatment	X-Ray	Microscopic	Results
37602	W. F. 19	Humerus, upper end	Trauma, 2½ months	Explored	Polycystic	Giant cell areas in osteitis fibrosa	Well 2 years
32584	W. F. 22	Tibia, malleolus	Trauma, 6 months	Curetted	Polycystic	Hemorrhagic cysts with giant cell areas	Well 3 months
28609	W. F. 12	Fibula, upper end	Trauma, 6 weeks	Resected	Polycystic	Small cysts surrounded by giant cell areas	Well 8 years
26053	W. F. 22	Finger, phalanx	Tumor, 6 months	Amputated	Polycystic	Hemorrhagic cysts surrounded by giant cell areas	Well more than 1 year
13214	W. M. 43	Femur, lower end	Tumor, 6 months	Resected	Polycystic	Multiple cysts with giant cells	Well 8 years
12207	W. F. 5	Tibia, upper end	Fracture, 16 months	Curetted	Polycystic	Small cysts surrounded by giant cell areas	Well 26 years
11466	W. M. 23	Tibia, malleolus	Tumor, 4 years	Curetted	Polycystic	Hemorrhagic cysts surrounded by giant cell areas, fibrous stroma	Discharged, well
5699	W. M. 22	Femur, trochanter	Fracture, 5 months	Curetted	Polycystic	Cysts surrounded by giant cell areas	Well 16 years
				Multiple Bone Involvement			
37250	W. F. 21	Humeri, tibia, radius	Tumor, 3 years	Explored	Polycystic	Small cysts surrounded by giant cell areas	Well 3 years
33358	W. F. 34	Humerus, tibia	Trauma, 3 years	Curetted	Polycystic	Small cysts surrounded by giant cell and spindle cell areas	Unimproved
32732	W. F. 5	Tibia	Tumor, 3 years	Explored	Polycystic	Cysts surrounded by giant cell areas	Well 5 years
29834	C. M. 12	Tibia, fibula, foot	Trauma, 6 months	Curetted	Polycystic	Hemorrhagic cysts within giant cell areas	Discharged, well

formation of cartilage to bone taking place in this locality has some bearing on the pathologic process involved.

In the x-ray picture and in the gross this group of lesions is inclined to be more subcortical than central in location, and the structure is most frequently multilocular. When this polycystic character was particularly marked under the microscope, the lesions were grouped separately under the classification of polycystic osteitis fibrosa.

On microscopic examination the present group of cases of osteitis fibrosa contain giant cells which are smaller, have fewer nuclei and are more sparsely distributed than one would expect for a typical giant cell tumor located in an epiphysis. In the stroma, too, there are more fibro-

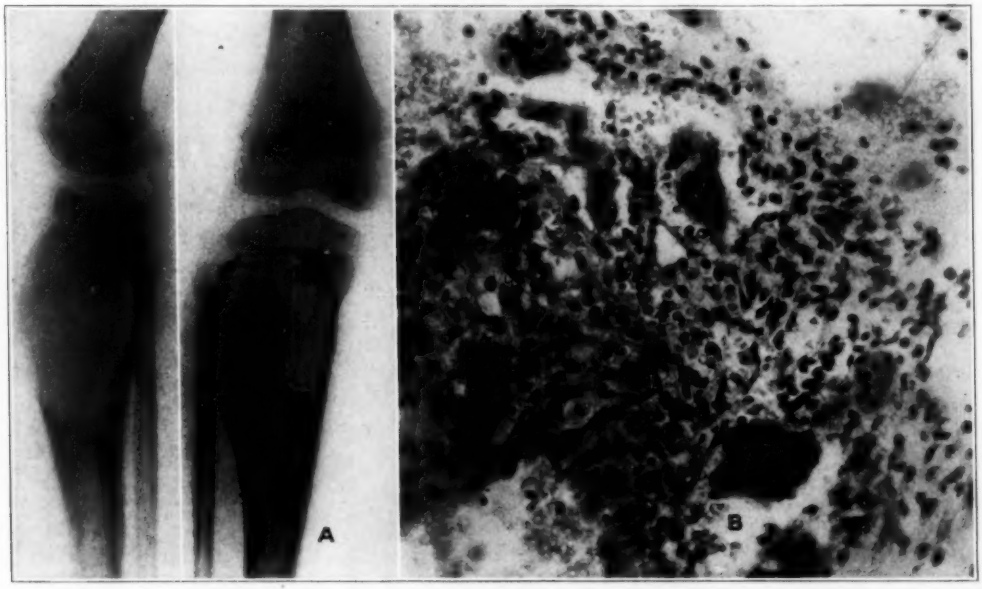

Fig. 9 (no. 34990).—A giant cell variant of osteitis fibrosa in the metaphysis (x-ray picture and section from the same case). *A*, the lateral and anterior x-ray views showing the typical fusiform lesion of the bone cyst extending to the epiphyseal line. The duration of symptoms was four months. *B* is a photomicrograph of one of the numerous giant cell areas found amid the osteitis fibrosa tissue in this lesion, demonstrating the tendency of the bone cyst to assume a giant cell structure when it borders on the epiphyseal line in an early stage of the disease.

blasts, more intercellular substance and more bone islands. However, small areas of larger giant cells surrounded by a narrow zone of round cells are met with here and there in the sections (fig. 9 *A* and *B*). Hemorrhages are a rather prominent feature of these lesions, and here the giant cells are apt to dispose themselves about the hemorrhage and about the cyst wall. The bone islands are the same as those found in osteitis fibrosa and are surrounded by osteoblasts.

The relation of this histologic picture to the relatively brief duration of the symptoms is again brought out by the recent cases referred to the surgical pathologic laboratory for diagnosis. Since patients have been consulting the physician more promptly during the last decade than ever before, sections from exploratory operations on bone cysts have shown, almost without exception, the inclusion of giant cell areas in the osteitis fibrosa tissue.

Polycystic Osteitis Fibrosa.—Two views may be taken concerning these lesions which are generally referred to by the name of polycystic osteitis fibrosa. One view is that they are an early stage of osteitis fibrosa, assuming a structure characterized by an aggregation of small cysts because a fusion of these small cavities at a later date represents the mode of origin of the large solitary cysts. The second view would be that such lesions are a more progressive form of bone cysts, and that their continued growth by the apparent budding of small cavities represents a transition between the solitary bone cyst (which is an arrested lesion) and the multiple form of osteitis fibrosa which is undoubtedly progressive. Some truth resides in both these views.

A survey of the cases in our series and those from the literature shows that in a large portion of cases the multiple bone cysts take on the structure of polycystic lesions. Hence, this peculiar multilocular structure is associated with the invasive nature of generalized osteitis fibrosa. On the other hand, when this polycystic structure is observed in a single bone (fig. 10 *A* and *B*), these lesions occur near the epiphyseal line in the metaphysis indicating an early stage in the transition from giant cell tumor to an arrested cyst. The most important feature, however, of this polycystic structure is that under the microscope these small cysts are surrounded by tissue rich in large multinucleated giant cells (fig. 31). This microscopic structure shows that elements of the bone destructive lesion of giant cell tumor persist and that the arrested stage characterized by fibro-ostosis and a scarcity of giant cells has not yet been reached. This lack of complete healing is explained on the one hand by the short duration of the symptoms and the proximity of the lesions to the epiphyseal line and on the other hand by the presence of multiple bone involvement indicating a generalized disease of the skeleton (table 3).

Knaggs,[16] in his excellent review of osteitis fibrosa, stated that he was convinced that there is an earlier bone destroying stage in the pathologic process of bone cysts which is responsible for these lesions. He remarked, however, that he had never seen such an early stage nor a description of it in the literature. This early stage, we believe, is seen in all giant cell variants of osteitis fibrosa, and nowhere is it better exemplified than in this particular group of polycystic lesions known to

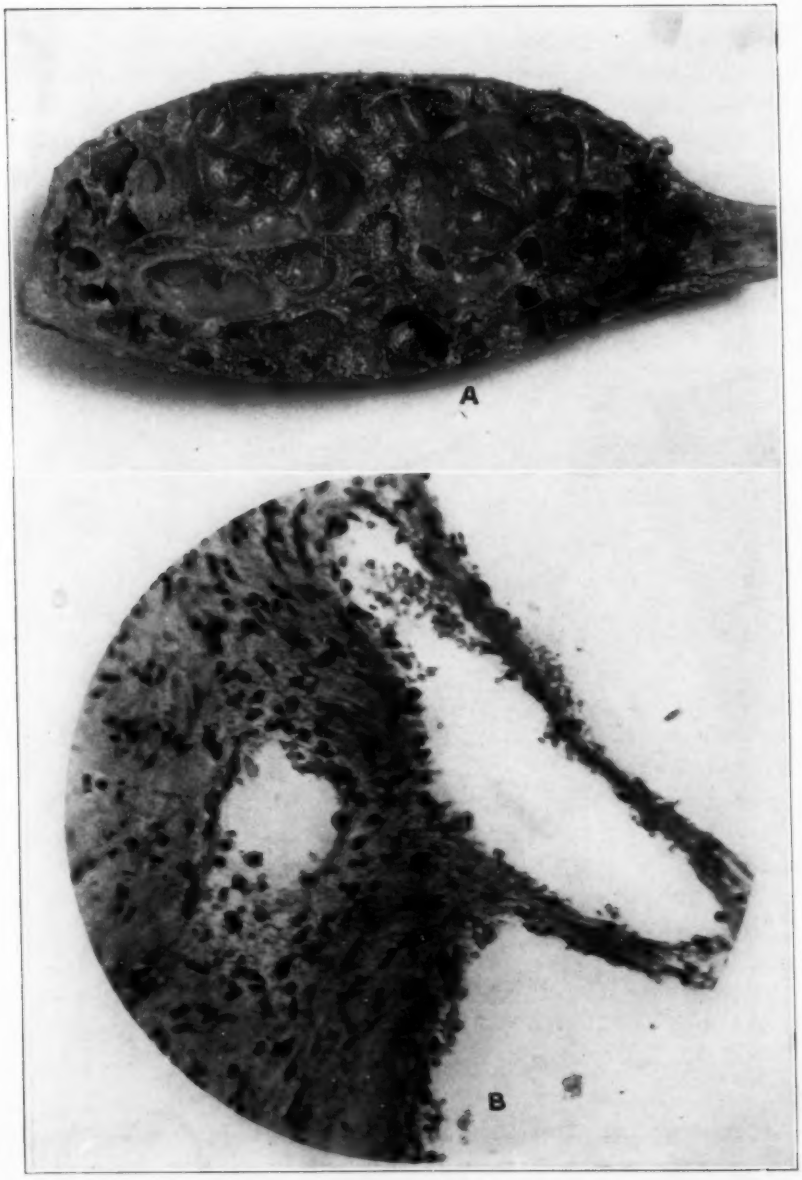

Fig. 10 (no. 28609).—*A*, polycystic osteitis fibrosa invading the epiphysis of the fibula; *B*, photomicrograph showing beginning of fusion in several small cavities. Note the association of red blood cells with the cysts.

the literature for over twenty-five years. The failure of the pathologic changes in this lesion to show its earliest stages has not been in the tumor but rather on the part of the pathologists in failing to recognize the significance of the histologic picture. This conclusion is justified by the appearance not only microscopically but also clinically. The duration of symptoms in this group of lesions when they occur singly near an epiphysis averages about five months compared to two and a half years for the typical bone cysts if one or two unusual cases are omitted. In the x-ray picture too, these lesions are found most often to be situated in a subcortical location rather than centrally, and this asymmetrical position is characteristic of both early giant cell tumors and early bone cysts as will be demonstrated later. From a histologic standpoint, the picture of multiple small cysts frequently filled by hemorrhage and sur-

TABLE 4.—*Location of Typical Giant Cell Tumors*

	Present Series*	Christensen's Series (Ann. Surg. **81** : 1074, 1925)
1. Upper tibia	39	53
2. Lower femur	36	87
3. Lower radius	32	30
4. Lower ulna	9	13
5. Upper humerus	5	22
6. Lower tibia	5	9
7. Upper femur	5	11
8. Upper ulna	3	4
9. Upper fibula	3	12
10. Upper radius	2	1
11. Scapula	2	6
12. Rib	2	7
13. Lower fibula	1	3
Total	144	258

* All the lesions listed were in an epiphysis.

rounded by giant cells exhibited by this group of tumors has all the characteristics essential to the interpretation of it as a transitional form between the giant cell tumor and the bone cyst.

GIANT CELL TUMOR

Since an examination of the giant cell variant and polycystic forms of osteitis fibrosa leads to the conclusion that giant cell tumor tissue is the earliest phase in the pathologic process of bone cyst, an analysis of the typical giant cell tumor is in order. From its relationship to the bone cyst it is to be inferred that this typical giant cell tumor is an entity with a shorter duration of symptoms, with a tendency to involve bone newly formed from cartilage (in an epiphysis), and that it is primarily a bone destructive lesion with a slighter degree of healing reaction of the same "fibro-ostosis" character. Such inferences are confirmed by an analysis of more than 200 giant cell tumors reported in the following tables.

Clinical Features.—Clinically, the giant cell tumor is a progressive, bone destroying lesion occurring at any age in the epiphysis, where osteo-

TABLE 5.—*Typical Giant Cell Tumor*

Path. No.	Race, Sex, Age	Location *	Symptoms	Fracture	Treatment	X-Ray	Microscopic	Results
43165	C. F. 38	Femur, lower end	.....	0	Curetting	.....	Typical giant cell areas	Discharged well
42119	F. 14	Radius, shaft and upper end	.....	0	Resection	Bone shell intact	Fibrous reaction at capsule	Discharged well
42429	W. F. 18	Tibia, right lower end	.....	0	Curetting	.....	Typical giant cell areas	Discharged well
40548	W. M. 23	Tibia, left upper end	Tumor 1½ years	0	Curetting	Bone shell intact	Typical giant cell areas	Discharged well
40168	M.	Radius, lower end	.....	0	Curetting	.....	Typical giant cell areas	Discharged well
40080	W. F. 18	Tibia, upper end	Tumor 2 months	0	Curetting	Bone shell intact	Typical giant cell areas	Discharged well
39682	W. M. 32	Tibia, upper end	Tumor 6 months	0	Curetting	Bone shell intact	Typical giant cell areas	Discharged well
39546	W. F. 25	Femur, right lower end	Pain 2 years	8 mos.	X-ray	Bone shell intact	.....	Well less than 5 years
39484	W. F. 15	Scapula, left, neck	Pain	0	Curetting	Bone shell intact	.....	Well less than 5 years
39242	W. M.	Ulna, right lower end	Trauma 3 months	0	Curetting	.....	Fibrous reaction at capsule	Discharged well
39004	W. F.	Femur, lower end	.....	Yes	.....	.....	.....	Well less than 5 years
38570	W. F. 21	Radius, left lower end	Tumor 7 weeks	0	.....	Bone shell intact	.....	Discharged well
38016	W. F. 28	Femur, lower end, left	Trauma 8 months	0	Curetting	Bone shell intact	.....	Well less than 5 years
38014	W. M. 32	Tibia, left upper end	Trauma 8 months	0	Curetting	Bone shell perforated	Typical giant cell areas	Discharged well
37933	W. M. 12	Femur, head	Tumor	0	Exploration	.....	Typical giant cell areas	Discharged well
37700	21	Humerus, right upper end	.....	0	.....	Bone shell intact	.....	Discharged well
37360	W. F. 23	Femur, right lower end	Pain 8 months	6 wks.	Amputation	Bone shell perforated	Typical giant cell areas	Discharged well
36668	W. F. 21	Tibia, left lower end	Pain 9 months	0	Curetting	Bone shell intact	Typical giant cell areas	Well less than 5 years
36440	W. F. 23	Femur, left lower end	.....	0	Refused	Bone shell perforated	.....	.....
36410	M.	Radius, left lower end	.....	Yes	Curetting	Bone shell perforated	Typical giant cell areas	Well less than 5 years
36358	W. F. 32	Tibia, right upper end	Trauma 22 months	0	Exploration	Bone shell perforated	.....	Discharged well
35902	W. F. 21	Radius, left lower end	Trauma 6 months	0	X-ray	Bone shell perforated	.....	Well less than 5 years
35862	W. M. 43	Tibia, left upper end	Trauma 18 months	0	Refused	Bone shell perforated	.....	.....
35754	W. F. 25	Fibula, left upper end	Tumor 13 months	0	Amputation	Bone shell intact	.....	Well less than 5 years
35562	W. M.	Tibia, left lower end	.....	0	Curetting	Bone shell intact	.....	Discharged well
35464	W. F. 18	Femur, left upper end	.....	0	Exploration	Bone shell intact	Fibrous reaction at capsule	Well less than 5 years
35114	W. F. 19	Femur, lower end	Pain 4 years	0	Curetting	.....	.....	Well more than 5 years
35112	W. F. 40	Tibia, upper end	.....	0	Amputation	Bone shell intact	.....	Well 10 years
35102	W. F. 29	Tibia, lower end	Trauma 8 months	0	Curetting	Bone shell perforated	.....	Well less than 5 years
35100	W. F. 53	Femur, lower end	.....	0	Amputation	.....	.....	Died of other causes
35098	W. F. 29	Tibia, upper end	Tumor 3 months	0	X-ray	Bone shell perforated	.....	Well less than 5 years
34990	W. F. 7	Tibia, left upper end	Trauma	0	Curetting	Bone shell perforated	Fibrous reaction at capsule	Well 5 years
34874	W. F. 26	Ulna, lower end	Trauma 18 months	0	Resection	Bone shell intact	Typical giant cell areas	Well less than 5 years
34542	W. F. 57	Femur, upper end	Pain 5 months	Yes	X-ray	Bone shell intact	.....	Discharged well
34348	W. F. 17	Tibia, right upper end	.....	.....	Curetting	Bone shell intact	.....	Well 5 years
34176	W. F. 14	Femur, upper end	Pain 1 year	0	Curetting	Bone shell perforated	Fibrous reaction at capsule	Well 5 years

34004	W. M. 36	Femur, right lower end	Pain 15 months	0	Curetting	Bone shell perforated	.....	Well 5 years
33748	W. M. 26	Radius, lower end	Tumor 4 months	0	Curetting	Bone shell intact	Typical giant cell areas	Well less than 5 years
33500	W. M. 29	Ulna, left lower end	Pain 6 months	Yes	Amputation	Bone shell perforated	Typical giant cell areas	Well more than 5 years
33061	W. M. 22	Tibia, right upper end	Tumor 8 months	.....	Curetting	Bone shell perforated	.....	Well 5 years
33277	W. M. 28	Tibia, left upper end	Pain 2 years	0	Amputation	Bone shell intact	Typical giant cell areas	Well more than 5 years
32039	.....	Tibia	.....	0	Amputation	.....	.....	Well more than 5 years
31970	W. F. 52	Femur, left lower end	Trauma 6 months	0	Curetting	Bone shell perforated	Typical giant cell areas	Well more than 5 years
31921	W. F. 35	Radius, right lower end	Tumor 4 months	Yes	Curetting	Bone shell perforated	Typical giant cell areas	Well less than 5 days
30368	W. F. 27	Scapula	Pain 2 years	Yes	Resection	Bone shell perforated	.....	Well more than 5 years
30315	C. M. 38	Ulna, upper end	Pain 18 months	0	Resection	Bone shell intact	.....	Well 10 years
30256	W. M. 14	Radius, lower end	Trauma 6 weeks	0	Curetting	.....	.....	Well 10 years
30187	W. F. 23	Femur, upper end	Trauma 6 years	Yes	Excision	Bone shell intact	.....	Well more than 5 years
30185	W. M.	Humerus, upper end	Trauma 10 months	0	Amputation	Bone shell intact	.....	Well 10 years
30172	W. F. 18	Fibula, right upper end	Pain 2 months	0	Excision	.....	.....	Well less than 5 years
30069	W. M. 22	Tibia, left upper end	Tumor 2 years	0	Curetting	Bone shell perforated	.....	Well more than 5 years
29718	W. F. 28	Femur, lower end	.....	Yes	Amputation	Bone shell intact	.....	Well more than 5 years
29715	W. M. 32	Radius, lower end	Trauma 8 months	0	Curetting	.....	.....	Well 10 years
29721	W. F. 73	Tibia, upper end	Trauma 1 year	0	Curetting	Bone shell perforated	Typical giant cell areas	Well more than 5 years
29674	W. F. 38	Rib, tenth posterior	Pain 6 years	0	Resection	Bone shell perforated	Typical giant cell areas	Well more than 5 years
29419	W. M. 29	Tibia, upper end	Trauma 9 years	0	Curetting	Bone shell intact	.....	Well 10 years
29409	W. M. 31	Tibia, right upper end	Pain 1 year	0	Curetting	Bone shell perforated	Typical giant cell areas	Well more than 5 years
29408	W. F. 28	Radius, left lower end	Tumor 6 months	0	Exploration	Bone shell perforated	.....	Well more than 5 years
29365	F.	Humerus, right upper end	.....	Yes	Curetting	Bone shell perforated	.....	Well more than 5 years
29364	M.	Femur, left lower end	Tumor	0	Curetting	.....	....	Well less than 5 years
29129	M.	Tibia, right upper end	Trauma 3 years	0	Refused	.....	.....	No information
28872	W. F. 51	Ulna, right upper end	.....	0	Curetting	Bone shell intact	.....	Well more than 5 years
28573	W. M. 37	Femur, left lower end	Trauma 1 year	0	Amputation	Bone shell perforated	Typical giant cell areas	Well more than 5 years
28399	W. M. 12	Humerus, upper end	Tumor 1 year	0	Curetting	Bone shell intact	.....	Well less than 5 years
28235	W. M. 35	Tibia, left upper end	Pain 9 months	0	Curetting	.....	Fibrous reaction at capsule	Well more than 5 years
28107	.....	Tibia, upper end	.....	0	Amputation	Bone shell perforated	Fibrous reaction at capsule	Discharged well
27897	W. F. 25	.....	Tumor 5 weeks	0	Amputation	Bone shell perforated	.....	Well 10 years
27605	W. M. 20	Femur, right lower end	Pain 1 year	0	Refused	Bone shell intact	.....	Well more than 5 years
27604	W. F. 20	Tibia, upper end	Pain 1 year	0	Resection	Bone shell intact	Fibrous reaction at capsule	Well 10 years
27563	W. M. 45	Radius, left lower end	Trauma 19 months	0	Curetting	Bone shell perforated	.....	Well 10 years
27318	.....	Tibia, upper end	.....	0	.....	.....	Typical giant cell areas	Discharged well
27116	W. F. 26	Femur, right lower end	Pain 6 months	0	Amputation	Bone shell perforated	Typical giant cell areas	Well more than 5 years
27059	.....	Radius, upper end	.....	0	Curetting	.....	Fibrous reaction at capsule	Well more than 5 years

* All the lesions listed were in an epiphysis.

TABLE 5.—*Typical Giant Cell Tumor—Continued*

Path. No.	Race, Sex, Age	Location*	Symptoms	Fracture	Treatment	X-Ray	Microscopic	Results
27001	W. M. 30	Tibia, left upper end	Pain 16 months	0	Resection	Bone shell perforated	Typical giant cell areas	Well more than 5 years
26792	W. M. 16	Humerus, left upper end	Trauma 16 months	0	Curetting	Bone shell intact	Typical giant cell areas	Well more than 5 years
26639	W. M. 58	Ulna, right upper end	Tumor 1 year	0	Refused	Bone shell perforated	.....	Well less than 5 years
23638	M.	Tibia, upper end	Trauma	0	Amputation	Bone shell perforated	.....	Well less than 5 years
25869	W. F. 26	Tibia, upper end	Pain	0	Curetting	Bone shell intact	Typical giant cell areas	Well more than 5 years
25778	W. F. 23	Femur, right lower end	Trauma 2 years	Yes	Refused	Bone shell perforated	.....	Well more than 5 years
24997	W. F. 32	Radius, left lower end	Tumor 1½ years	0	Resection	Bone shell intact	.....	Well less than 5 years
24124½	.....	Ulna, lower end	.....	0	Resection	.....	.....	Well more than 5 years
23852	C. F. 23	Ulna, right lower end	Tumor 1 year	0	Resection	Bone shell perforated	Typical giant cell areas	Well less than 5 years
21522	C. F. 33	Fibula, right lower end	Tumor 6 years	0	Curetting	Bone shell perforated	.....	Well more than 5 years
20373½	W. F. 41	Femur, left lower end	.....	0	Amputation	.....	.....	Well more than 5 years
20115	W. M. 46	Femur, right lower end	.....	Yes	Amputation	Bone shell perforated	Typical giant cell areas	Well 10 years
19267	W. M. 11	Clavicle and first rib	Tumor 9 months	0	Resection	.....	.....	Well 10 years
17706	C. F. 49	Radius, left lower end	Pain 3 months	0	Resection	Bone shell intact	Fibrous reaction at capsule	Died of other causes
16720	W. F.	Radius, left lower end	Trauma 4 years	1 year	Resection	Bone shell intact	Typical giant cell areas	Well less than 5 years
16596	W. F. 24	Tibia, upper end	Tumor 18 months	0	Curetting	.....	Typical giant cell areas	Well less than 5 years
16560½	W. M.	Radius, lower end	.....	0	Resection	.....	.....	Discharged well
14550	W. F. 24	Tibia, left upper end	Pain 6 months	0	Curetting	Bone shell intact	.....	Well 10 years
14508	W. F. 19	Tibia, lower end	Trauma 2 years	0	Resection	.....	Fibrous reaction at capsule	Well more than 5 years
14421½	W. M. 40	Femur, lower end	Trauma 5 years	0	Curetting	Bone shell intact	.....	Well 10 years
13025	W. M. 34	Femur, right lower end	Pain 15 months	0	Curetting	.....	Typical giant cell areas	Well 10 years
12927	M.	Radius, right lower end	.....	0	Resection	Bone shell intact	.....	Well 10 years
12474	W. M. 48	Ulna, right lower end	Trauma 8 months	0	Resection	Bone shell perforated	Typical giant cell areas	Well more than 5 years
12276	W. M. 22	Tibia, left upper end	Pain 1 year	0	Resection	Bone shell perforated	Typical giant cell areas	Well more than 5 years
11855	W. F. 21	Fibula, right upper end	Trauma 7 months	0	Resection	Bone shell perforated	Typical giant cell areas	Well 10 years
11526	W. F. 27	Femur, lower end	Pain 2 years	0	Amputation	Bone shell perforated	Typical giant cell areas	Well 10 years
10975	W. F. 26	Tibia, upper end	Pain 39 months	0	Resection	Bone shell intact	Typical giant cell areas	Well 10 years
9073	W. M. 24	Ulna	Tumor 20 months	0	Resection	.....	Typical giant cell areas	Dead of other causes
8680	W. F. 72	Radius, right lower end	Trauma 8 years	0	Resection	Bone shell intact	Typical giant cell areas	Well 10 years
8666	W. F. 45	Femur, lower end	Pain 6 months	Yes	Amputation	Bone shell perforated	Typical giant cell areas	Dead of other causes
7831	W. F.	Femur, lower	.....	Yes	Amputation	Bone shell perforated	Fibrous reaction at capsule	Well 10 years
6125	W. M. 22	Radius, lower end	Pain 20 months	0	Resection	Bone shell perforated	Typical giant cell areas	Well 20 years
6022	W.	Radius, lower end	.....	0	Refused	Bone shell perforated	.....	Well 10 years
5601	W. F. 52	Radius, left lower end	Trauma 1 year	9 yrs.	Amputation	Bone shell perforated	.....	Well 10 years
4396	W. F. 22	Femur, lower end	Tumor 3 years	Yes	Amputation	Bone shell intact	Typical giant cell areas	Well 10 years
3623	W. M. 23	Femur, left lower end	Trauma 6 months	Yes	Amputation	Bone shell perforated	Typical giant cell areas	Well 10 years
2458	W. M. 29	Femur, lower end	Trauma 1 year	0	Amputation	.....	Typical giant cell areas	Discharged well
2420	W. M. 28	Radius, lower end	Tumor 7 months	0	Amputation	Bone shell perforated	Typical giant cell areas	Well 20 years
1815	W. M. 44	Radius, lower end	Pain 32 months	28 mos.	Amputation	Bone shell perforated	Typical giant cell areas	Well 20 years
738	W. M. 26	Radius, left lower end	Trauma 3 months	0	Amputation	.....	.....	Well 20 years
275	C. F. 45	Ulna, left lower end	Tumor 1 year	0	Resection	.....	Typical giant cell areas	Well more than 10 years

* All the lesions listed were in an epiphysis.

genesis proceeds until late in life. The maximum number of cases (40 per cent) occur in the third decade between the ages of 21 and 31 years, or about a decade later than the average bone cyst. This is in keeping with the difference in locality of the areas affected. Whereas the bone cyst favors the metaphyseal ends of the upper part of the humerus, femur and tibia, the giant cell tumor selects most frequently the epiphysis of the lower part of the femur and radius and the upper part of the tibia (table 4). Ossification in the epiphysis persists later in life than in the metaphyseal regions and accounts for the age difference between these two tumors.

Although the giant cell tumor is typically benign, case follow-ups show thirty-two recurrences in a series of 226 cases indicating that the tumor is usually progressive and must be eradicated by proper treatment. Omitting five cases which gave the unusual history of a duration of from six to nine years, the average time when the patient first came under observation was fourteen months after the onset, as compared with the average for the typical bone cyst of thirty months. The usual sequence of symptoms was trauma, pain, tumor and fracture—trauma being present in 42 per cent of the cases and pathologic fracture in 14 per cent (table 5).

X-Ray Features.—The x-ray pictures of this tumor emphasize its bone destructive character. The lesion generally assumes an asymmetrical position in an epiphysis, a comparison of early and late lesions showing that the area of bone destruction begins in a subcortical location at one side of the epiphysis and works its way toward a more central location at the expense of cancellous bone (figs. 11, 12 and 13). The expanded bony shell of the tumor is extremely thin and, in slightly less than 100 cases examined roentgenologically in this series, was found perforated in 60 per cent of the lesions. Trabeculae traverse the diameters of the tumor when the shell of bone is intact, but as the tumor becomes larger, the trabeculae and then the bone shell disappear, the tumor extending into the soft parts. Such extension is aided by pathologic fracture when it occurs (fig. 14 *A* and *B*). In even relatively advanced lesions there is no periosteal reaction, and central areas of new bone formation are wanting.

Gross Appearance.—The gross appearance of the typical giant cell tumor shows the same bone destruction featured in the x-ray pictures, but demonstrates more clearly the limited but definite healing reaction about the margin of the tumor. The gross appearance of the tumor mass itself is usually hemorrhagic in nature. As Bloodgood stated, it is usually like an old bruise, every grade from red to black, although occasionally it is a uniform gray, putty color. At the operation, when touched, it bleeds, oozing like a sponge. When crushed, it is friable like

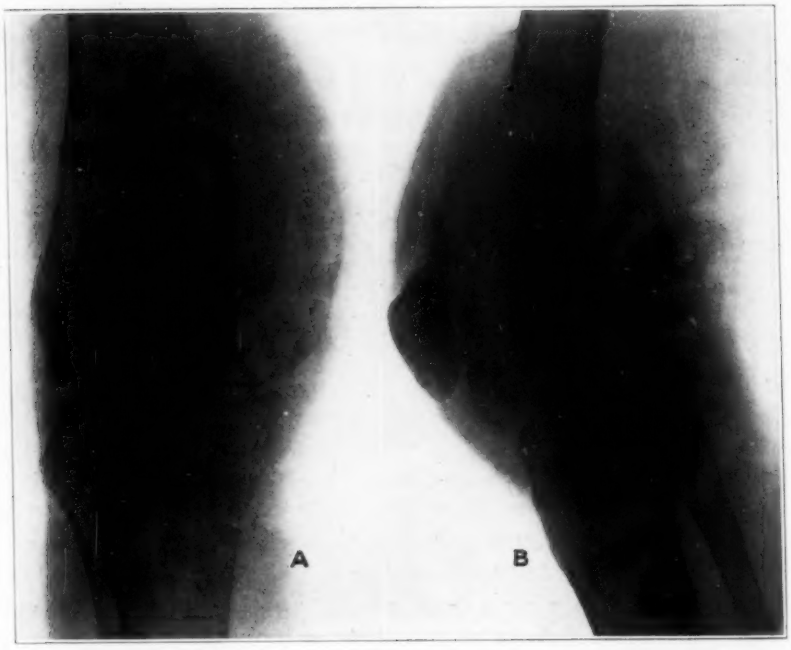

Fig. 11 (no. 25778).—*A*, anterior, and *B*, lateral x-ray views of a giant cell tumor in the lower end of the femur. Note the asymmetrical location of the lesion and the extreme thinness of the bone shell. The trabeculae have almost disappeared.

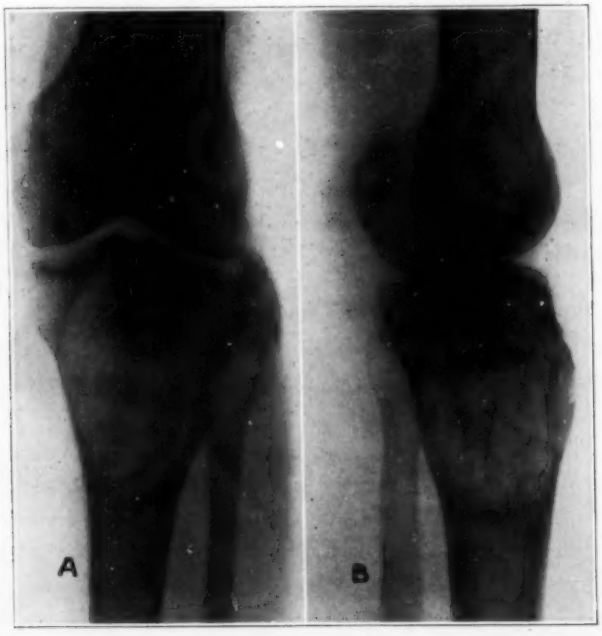

Fig. 12 (no. 32277).—*A*, anterior, and *B*, lateral x-ray view of a giant cell tumor in the upper end of the tibia. The bone shell is still intact; trabeculae are present.

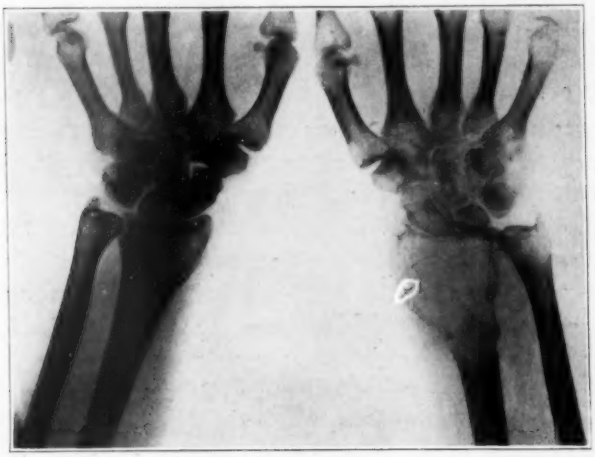

Fig. 13 (no. 37708).—Giant cell tumor in the lower end of the right radius. The bone shell is perforated on the lateral side, and the trabeculae there are disappearing.

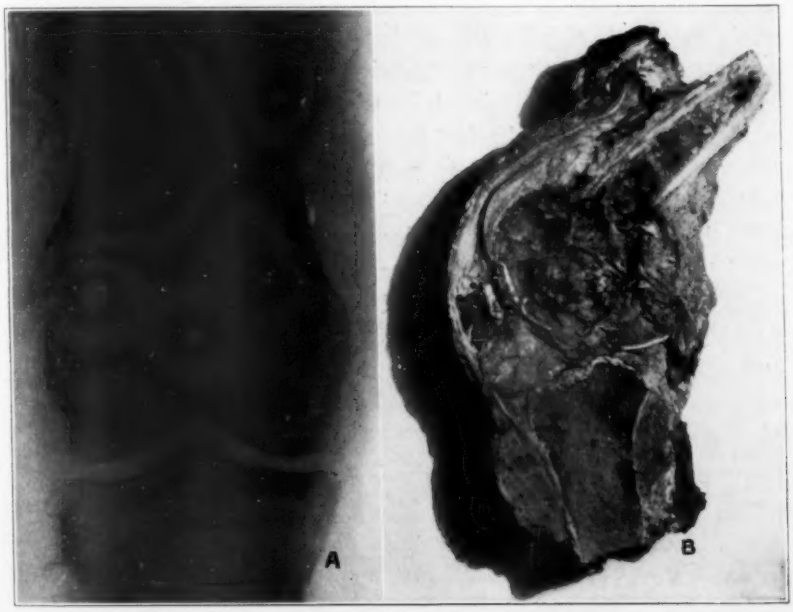

Fig. 14 (no. 37360).—*A*, x-ray picture, and *B*, gross specimen of a pathologic fracture through a giant cell tumor in the lower end of the femur. Fracture has aided the tumor in the invasion of the soft parts.

cheese. Fibrous areas may be palpated in the gross, extending inwardly like partitions from the capsule. These are the trabeculae seen in the x-ray picture, and under the microscope they are fibrous septums resembling osteitis fibrosa.

The encapsulation of the tumor mass is sometimes effected by a connective tissue envelope, resembling in many respects the leathery fibrous capsule of the bone cyst. In the gross, the reaction of fibro-ostosis is most pronounced in the cortical bone on the shaft side of the epiphysis. Here the cortical bone thickens and extends downward from the shaft toward the epiphysis preceded by fibrous tissue. The cancellous bone extending across the medullary cavity on the shaft side also lays down a fibrous barrier to the tumor which may result in a capsule visible in the gross, but more often discernible only under the microscope when sections are made from this region.

In the epiphysis itself, in which the tumor is situated, the lateral margins present contrasting reactions. Because of its asymmetrical position the tumor borders on cortical bone on its outer side in early lesions, while inwardly, cancellous bone is infiltrated. The border of cortical bone resists longer and more effectively the advances of the tumor. Its reaction consists in the laying down of new bone and fibrous tissue (fig. 15 *A* and *B*). The natural structure of cortical bone, however, is extremely thin in this region of the epiphysis as will be seen from figure 16, and ultimate perforation through its wall is by no means rare. The superiority of its defense over cancellous bone is demonstrated, nevertheless, by the fact that the tumor expands centrally to the opposite side of the epiphysis in most instances before the cortical shell gives way. The joint cartilage, to which point the lesion generally extends because of its epiphyseal location, resists successfully the invasion of the joint cavity. Its defense is by means of calcification of its already compact substance, the calcified tissue being transformed into bone (figs. 17 and 18).

Thus it will be seen that everywhere about the tumor normal structures are endeavoring to stem the invasion. When this reactive tissue is examined microscopically, it shows a histologic structure typical of the fibro-ostosis seen in the wall of the bone cyst. Indeed the microscopic structure of the giant cell tumor differs from that of the bone cyst, not in kind but only in degree. Here there is more giant cell tumor tissue and less fibro-ostosis, while in the bone cyst there is a preponderant fibrous proliferation and new bone construction with little or no remnant of giant cell tumor tissue. Microscopically, these giant cell areas represent the fundamental pathologic change underlying these lesions, and a careful study of them discloses the nature of giant cell tumor.

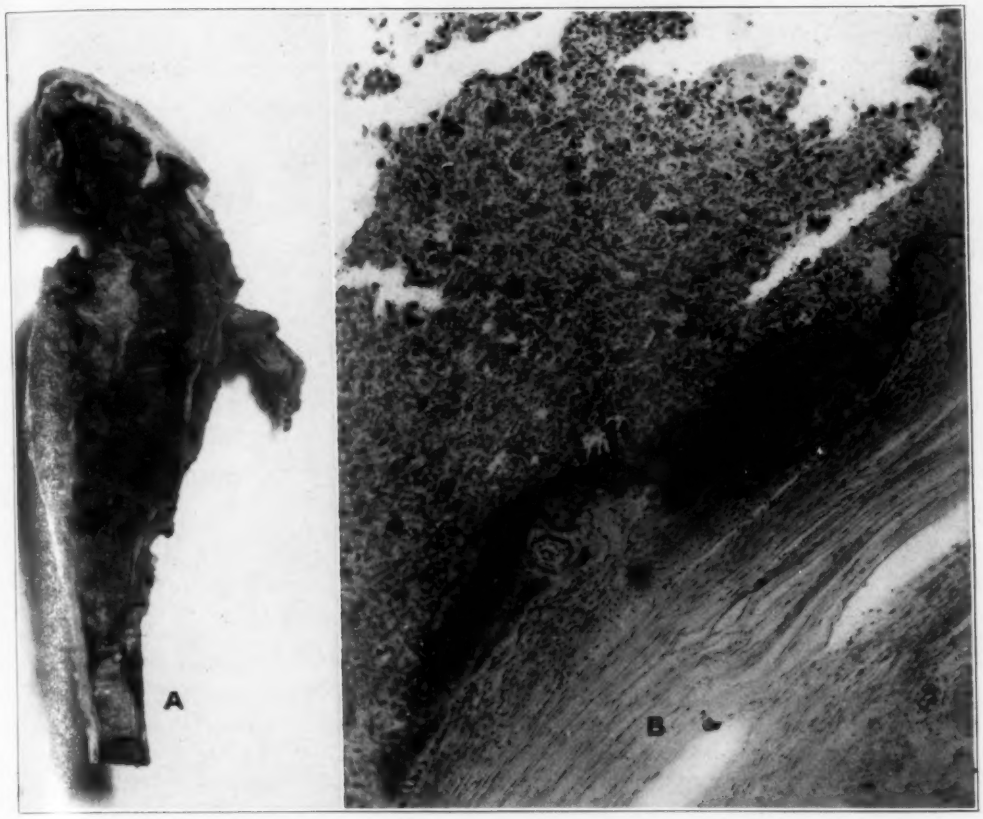

Fig. 15 (no. 32924).—*A*, gross specimen, and *B*, microscopic section of a giant cell tumor in the lower end of the fibula. The photomicrograph shows a reaction of new bone and fibrous tissue in the tumor capsule. The new bone has taken on a deep stain.

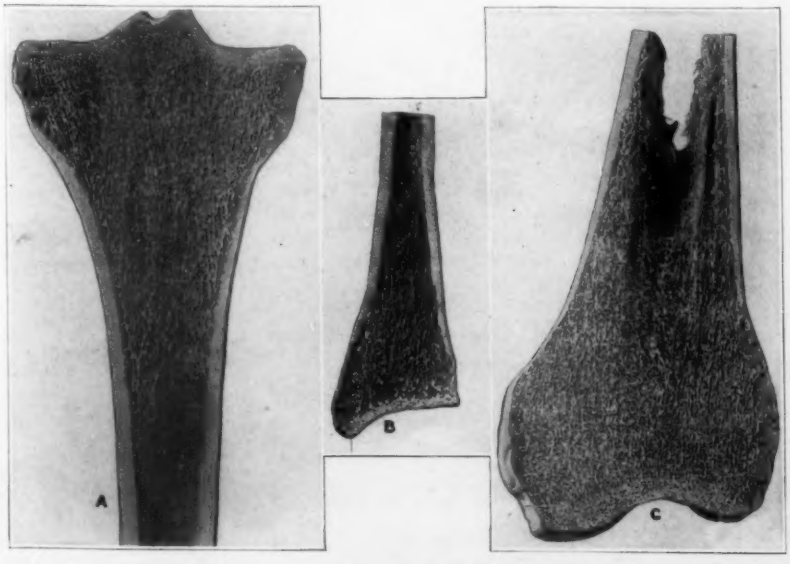

Fig. 16 (after Toldt).—The epiphyseal regions of the *A*, upper part of the tibia, *B*, lower part of radius and *C*, lower part of femur. Attention is directed to the normal cancellous structure of the epiphysis and the thinning of the cortex of compact bone and periosteum in these regions.

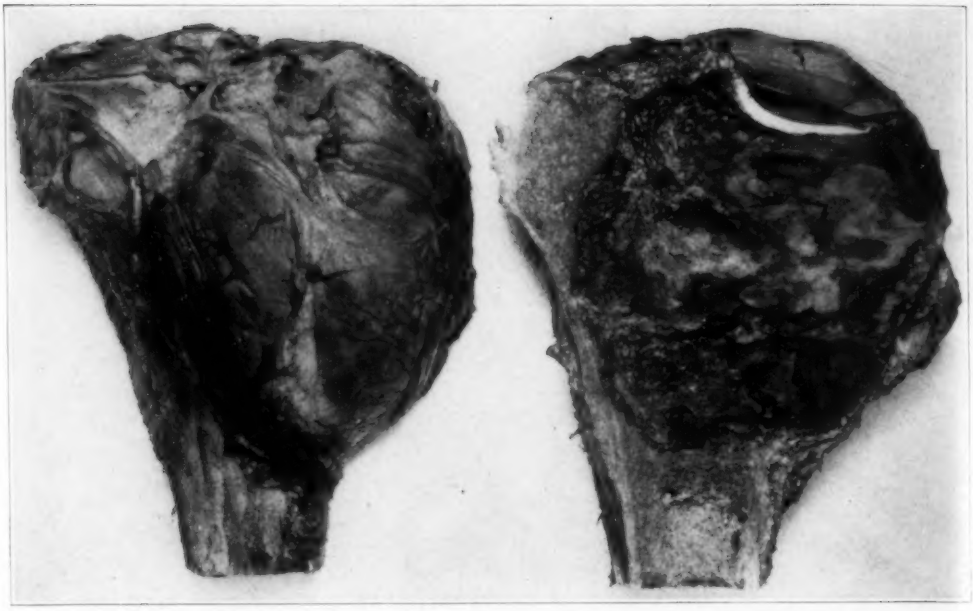

Fig. 17 (no. 27001).—Giant cell tumor in the upper end of the tibia. The tumor extends to the joint cartilage. No fibrous reaction is discernible here in the gross in the cut section. Fibrous tissue may be seen overlying the outer surface of the tumor on the uncut surface.

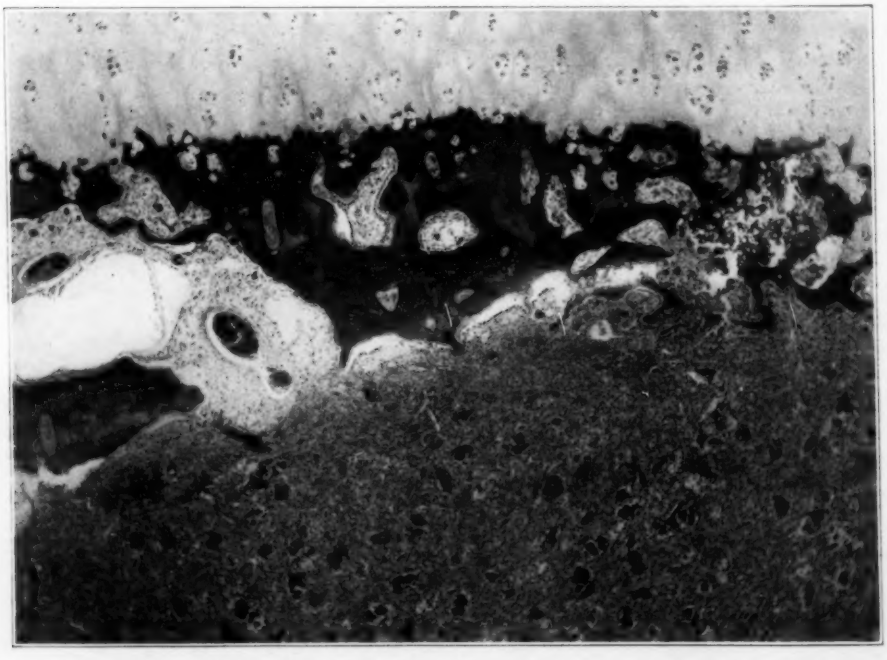

Fig. 18 (no. 10975).—Photomicrograph showing the reaction of joint cartilage. The cartilage has become calcified and is laying down compact bone to resist the invasion of the giant cell tumor.

Microscopic Analysis.—The tumor mass proper, of the typical giant cell tumor, which is responsible for the bone destruction observed in this lesion and also in the bone cyst, is composed essentially of large multinucleated giant cells embedded in a mass of smaller round cells (fig. 19 *A* and *B*). The giant cells average over 30 cells per field under the low power, with the number of nuclei in each cell varying from 15 to 200. The cells range in size from 10 to 100 microns and may or may not have distinct borders to the cytoplasm.

The number of giant cells present varies from field to field, being more numerous about areas of hemorrhage, about spicules of old bone or about the walls of minute cysts. The typical giant cell tumor, however, maintains with remarkable regularity, in most areas, a crowding of large multinucleated elements. Giant cells with few nuclei relatively small and sparsely distributed are not typical of the benign giant cell tumor and are more characteristic of the variants of osteitis fibrosa and osteogenic sarcoma (figs. 20 and 21).

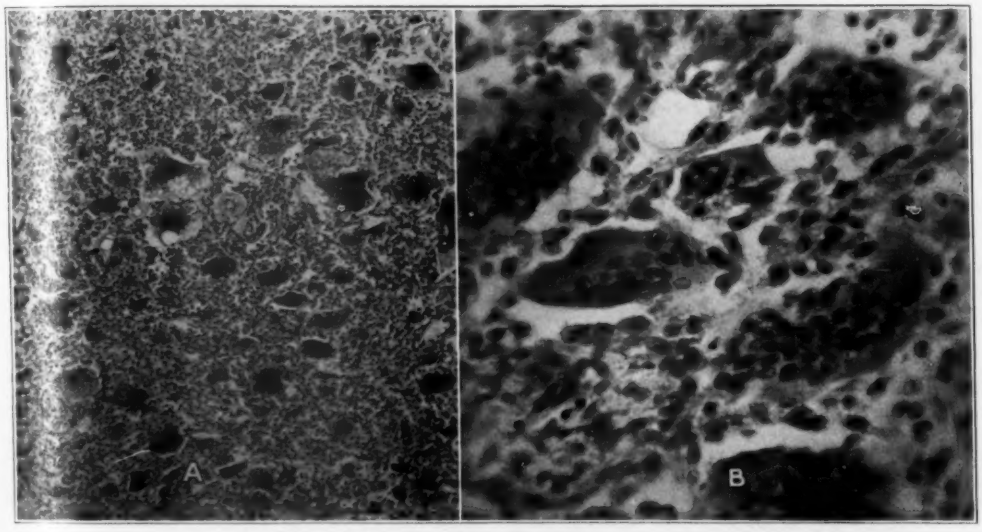

Fig. 19 (no. 37360).—*A*, low, and *B*, high power photomicrographs of the typical giant cell tumor. There are over thirty cells to the low power field and the usual number of nuclei is over fifteen per cell. In the high power it will be seen that round cells predominate the stroma.

An outstanding peculiarity of the typical giant cell tumor is the cellular stroma in which the giant cells are embedded. Two kinds of cells can always be found in this stroma, the round and spindle cell, but in the typical giant cell tumor group, the round cells outnumber the spindle cells in every instance. This small round cell has a relatively large nucleus and a small amount of cytoplasm. There is a definite

nuclear wall and a nucleolus. The nucleus is generally from 3 to 7 microns in size with a fairly large amount of chromatin evenly distributed, and the borders of the cytoplasm are usually indistinct.

There is, apparently, a definite relationship between the round cell of the stroma and the giant cell. In the first place, when the giant cell predominates the tumor by its numbers, the round cell prevails in the

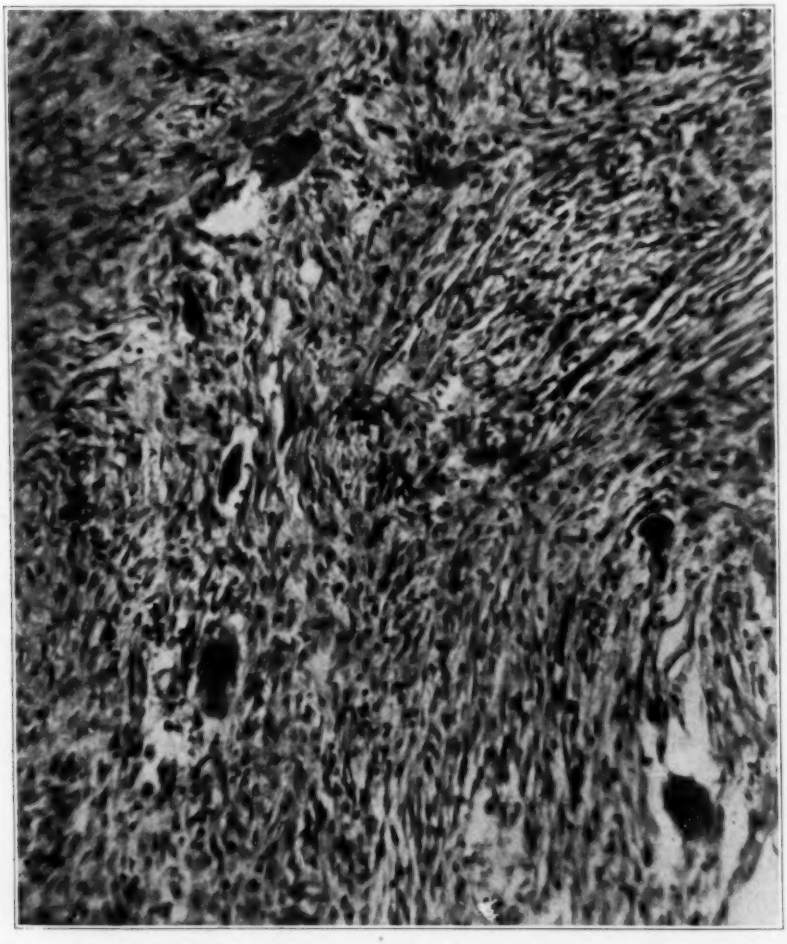

Fig. 20 (no. 32013).—The giant cell variant of osteitis fibrosa. Note the small size and scarcity of the giant cells and the large number of spindle cells and fibroblasts in the stroma. Microscopically, the tumor is benign.

stroma. Moreover, the nuclei of the giant cell always have the same general form and staining characteristics as the nuclei of the round cells. The only important variation is the tendency for the giant cells to have a more acidophilic cytoplasm with occasionally a greater concentration of chromatin in the nuclei and other signs of early degeneration. This

could be accounted for by a seniority in the age of the giant cell, the inference being that the giant cells are formed by agglutination of the round cells in the stroma.

Conspicuous in the histologic structure of giant cell tumor is hemorrhage. Red blood cells in a well preserved state infiltrate the tumor more often unenclosed by endothelial walls than otherwise. The typical

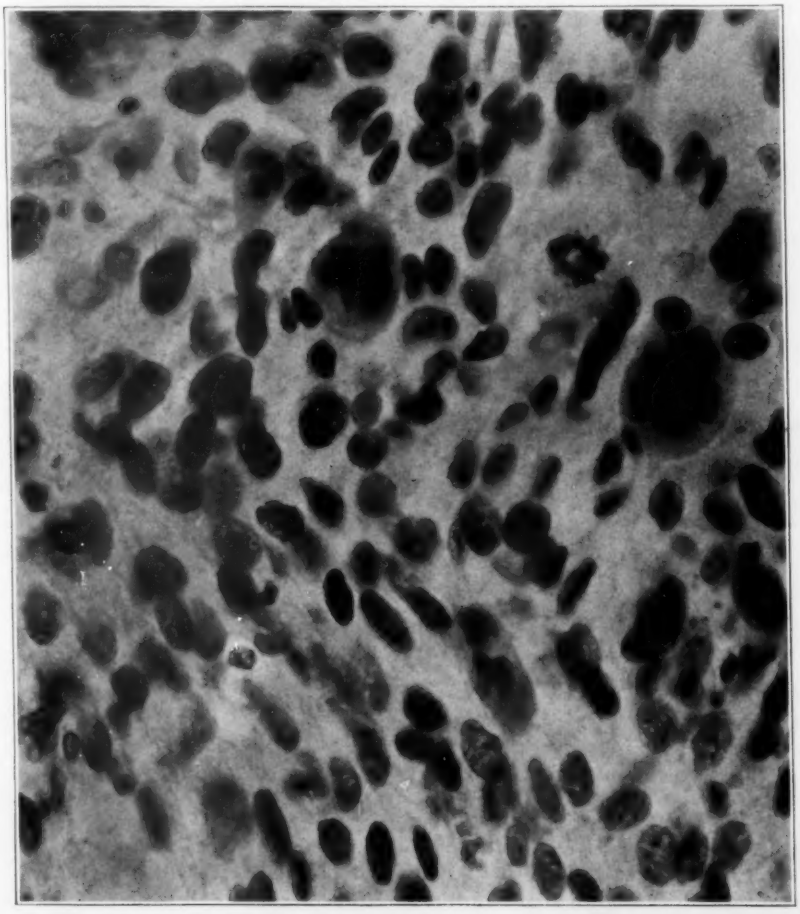

Fig. 21 (no. 39274 [B.T. 9]).—Osteogenic sarcoma with giant cells. Two giant cells are present in the field, each having less than fifteen nuclei. The most important diagnostic feature of the section is the presence of the large vesicular nuclei, some of which are undergoing mitotic division.

giant cell tumor is thus both hemorrhagic and vascular, newly formed vessels being by no means rare. Areas of organizing hemorrhage are frequent, and bordering on these is loose edematous tissue intermingled with areas of osteitis fibrosa.

Spicules of bone are frequently found near the margin of the tumor or at its capsule. Some of these spicules are undoubtedly surviving portions of old bone undergoing destruction (fig. 22), to be recognized by the giant cells applied to their surface, the condensation of calcium salts at the margins, the frayed and worn edges, and the small size of the bone cells included in the matrix of the spicules. Other spicules with osteoblasts applied to their surface are new bone resembling those frequently seen in osteitis fibrosa, and represent a healing reaction rather than bone of tumor origin.

Fig. 22 (no. 14229).—Spicules of old bone being attacked by giant cells. The margin of the spicules shows condensation of lime salts, worn and broken edges, and giant cell osteoclasts applied to the surface. The bone cells within the spicules are small, and fine linear markings are still present in the matrix.

The spindle cells conspicuous about the new bone spicules are found elsewhere in the tumor among the round cells of the stroma. They are oval and slender in form with a nucleus rather well defined and a cytoplasm elongated but sparse, without definite outlines. Fine fibrils surrounding these spindle cells indicate their fibroblastic tendencies and

identify them with the same type of cells seen in osteitis fibrosa. When these spindle cells predominate the stroma in giant cell tumor, they indicate a healing process and mark the section as a variant (the spindle cell or osteitis fibrosa variant) of the giant cell tumor. This important group of hybrid tumors demonstrates a transitional phase between giant cell tumor and osteitis fibrosa.

TRANSITIONAL LESIONS BETWEEN THE GIANT CELL TUMOR AND THE BONE CYST

The so-called spindle cell variant of the giant cell tumor and the group of multiple giant cell tumors and multiple bone cysts demonstrate by their transitional structure the unity of the pathologic process underlying both the bone cysts and the giant cell tumor. These two transitional forms will be considered separately.

The Spindle Cell Variant of the Giant Cell Tumor.—It has been shown that the encapsulation of the giant cell tumor is accomplished by a healing reaction at its margin resembling in morphology, osteitis fibrosa. This healing reaction of fibro-ostosis predominates in sections taken from the margins of giant cell tumors, and for this reason twelve of the sixty cases graded as spindle cell variants of the giant cell tumor were found on further study to be taken from such areas in otherwise typical giant cell tumors. In this group of twelve cases a single section under the microscope would often show a giant cell area, a border of spindle cells, a further outlying zone of osteitis fibrosa and a final region of proliferating cortical bone, demonstrating clearly the nature of the healing reaction and the attempt by nature to lay down a defensive wall (fig. 23).

A special investigation was undertaken to verify this interpretation of the spindle cell tissue as a healing reaction. Blocks for sectioning were taken from various portions of the tumor margin in thirty gross specimens and examined. Sections taken from the region of cortical bone on the shaft side of the giant cell tumors always showed a marked protective reaction, histologically resembling in every respect fully developed osteitis fibrosa. The same was true of sections taken from a well formed connective tissue capsule, particularly where the periosteum joined in the formation of the capsule. When other sections were made from the region of cancellous bone either in the epiphysis or in the medullary cavity on the shaft side of the tumor, the defensive reaction was less pronounced but evident, and the infiltrating areas of giant cells in fibrous tissue gave the histologic picture typical of what has been called the spindle cell variant (fig. 24). Even when sections were taken at the point where tumor perforated and infiltrated into the soft parts, there was the same fibrous reaction, although under the microscope

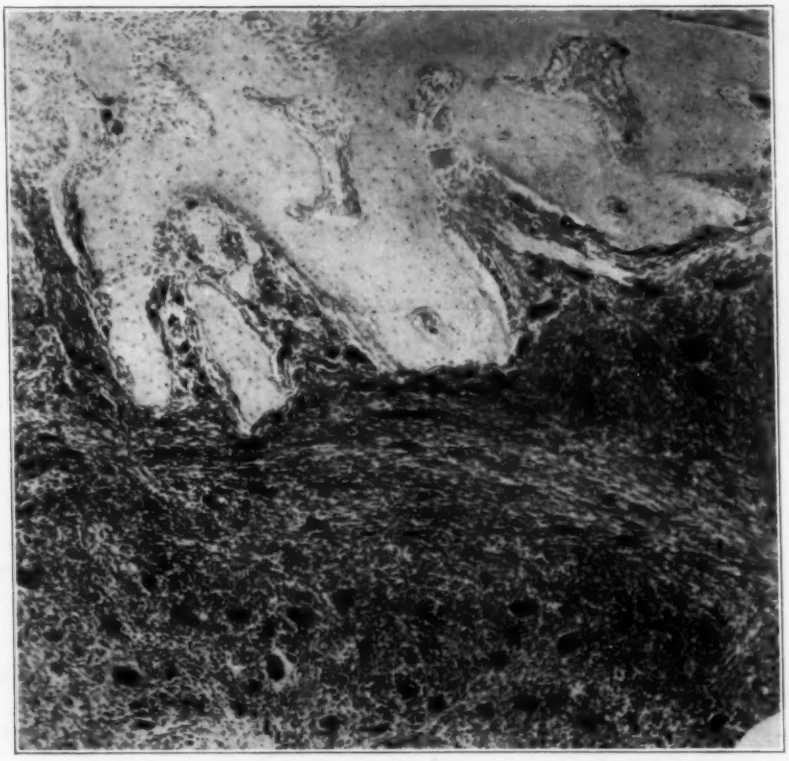

Fig. 23 (no. 17706).—Section taken from the periosteal margin of a giant cell tumor. New bone formation preceded by a layer of fibrous tissue is attempting to wall off the tumor.

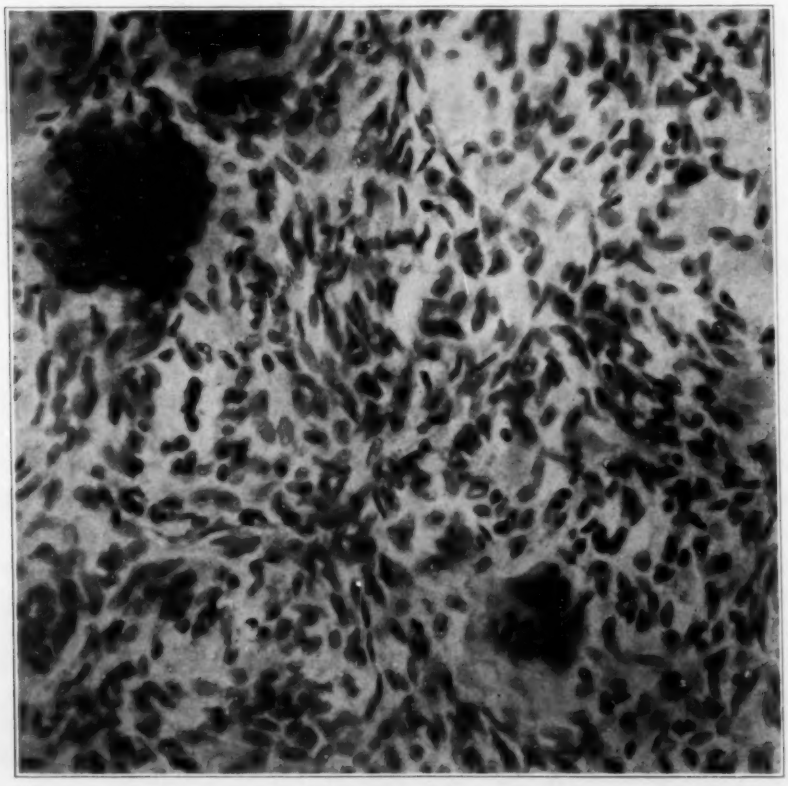

Fig. 24 (no. 11855).—A giant cell tumor showing spindle cell variation near the tumor margin. Spindle cells are infiltrating about the large giant cells.

avenues had been opened up in this tissue through which giant cells were streaming (fig. 25). Even on the cartilage side of the tumor margin toward the joint, the reaction was evident, calcified cartilage with transition to compact bone abutting on tumor area.

In thirty-seven cases showing this spindle cell variation under the microscope (tables 6 and 7), the fibroid change was fairly uniform throughout the tumor. This group of cases was of unusual interest because histologically it was practically impossible to make the distinction between giant cell tumor and bone cyst. Clinically, they were all

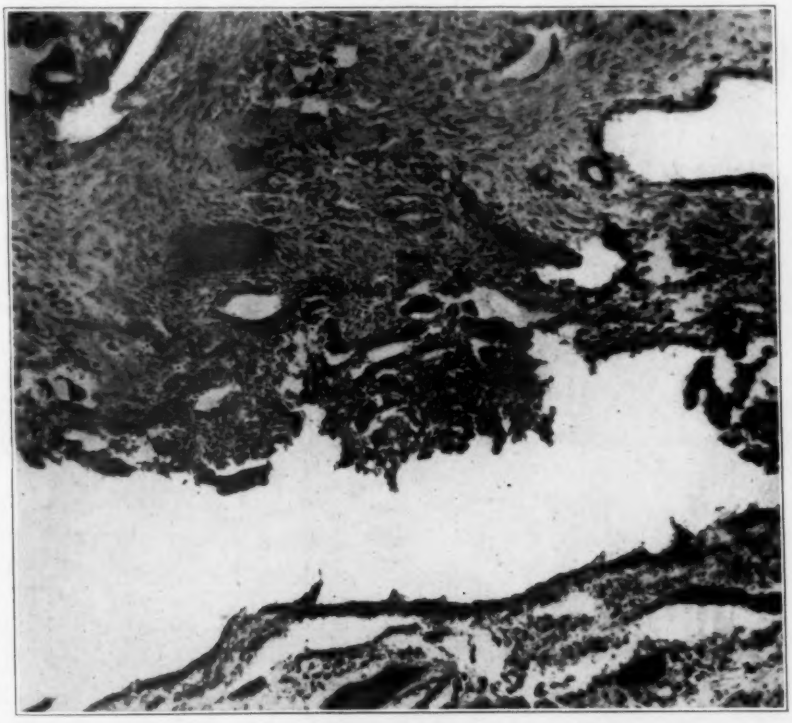

Fig. 25 (no. 26091).—Giant cells perforating the new bone of the tumor capsule. The channel in the lower portion of the picture is the line of perforation. The giant cells are deeply stained, and no definite structure is visible. The poor staining is due to the age of the specimen from which this particular area was selected for sectioning.

located in bones other than the long pipe bones, eight were in the vertebrae and twenty-nine were in the small bones of the hands and feet or in the flat bones. The interpretation placed on these lesions was that they represented giant cell tumors in which the healing reaction was unusually prominent. The clinical follow-up on this group of cases confirmed this. None of these patients died of tumor if we may except one which proved inoperable when a laminectomy was attempted on a

TABLE 6.—*Spindle Cell Variants of Giant Cell Tumors in the Small Bones*†

Path. No.	Race, Sex, Age	Location	Symptoms	X-Ray	Treatment	Microscopic	Results
39514	W. M. 60	Hand, phalanx	Pain 6 years	Bone shell intact	X-ray	Spindle cell stroma	Discharged well
35174	W. F. 30	Metatarsal, tarsal	Tumor 1 year	Bone shell intact	Curetting	Spindle cell stroma	Well less than 5 years
35110	W. F. 46	Hand, phalanx	Trauma 6 months	Bone shell perforated	Amputation	Spindle cell stroma	Well more than 5 years
33346	W. F. 10	Metacarpal, carpal	Tumor 10 weeks	Bone shell intact	Excised	Spindle cell stroma	Well less than 5 years
32209	W. F. 17	Metacarpal, carpal	Tumor 6 months	Bone shell perforated	Amputation	Spindle cell stroma	Well more than 5 years
29103	W. F. 38	Metatarsal, tarsal	Tumor 13 years	Multiple, encapsulated	Resected	Spindle cell stroma	Well more than 5 years
24682	W. M. 34	Metacarpal, carpal	Tumor 10 months	Bone shell perforated	Amputation	Spindle cell stroma	Well less than 5 years
17536	M.	Foot, phalanx	No note	No note	Amputation	Spindle cell stroma	Discharged well
17436	W. F. 41	Oscalcis	Trauma 3 years	Multiple, encapsulated	Curetted	Spindle cell stroma	Well 10 years
17009	26	Astragalus	Tumor	No note	Resected	No note	Well 5 years
16725	W. M. 30	Astragalus	Pain	Bone shell intact	Curetted	Spindle cell stroma	Well 10 years
24122½	W. M. 33	Oscalcis	Trauma 9 months	Bone shell perforated	Curetted	Spindle cell stroma	Well 10 years
33572	W. F. 22	Vertebra, 5th lumbar	Trauma 8 months	Multiple, encapsulated	Curetted	Spindle cell stroma	Discharged well
38530	W. F.	Vertebra, 3d lumbar	Tumor	No note	Explored	Spindle cell stroma	Unimproved
30181*	W. M. 16	Vertebra, 10th dorsal	Trauma 3 months	Bone shell intact	Resected	Spindle cell stroma	Well more than 5 years
29716*	W. M. 14	Vertebra, 4,5 lumbar	Trauma 7 weeks	No note	Curetted	No note	Well more than 5 years
29452	W. F. 8	Vertebra, 2,3 dorsal	Paraplegia 1 month	Bone shell intact	Curetted	Spindle cell stroma	Well more than 5 years
16307	W. F. 11	Vertebra, 5th lumbar	Pain 5 months	No note	Curetted	Spindle cell stroma	Well when discharged
12838	.....	Vertebra	.....	.....	.....	Spindle cell stroma	Well less than 5 years
10694	W. M. 24	Sacrum, 5th lumbar	Paraplegia	No note	Explored	Spindle cell stroma	Dead of tumor

† In table 7 are shown lesions of a similar nature, with a greater healing reaction.

TABLE 7.—*Giant Cell Variant of Osteitis Fibrosa in the Small and Flat Bones*

Path. No.	Race, Sex, Age	Location	Symptoms	Treatment	Microscopic	Results
36614	W. M. 28	Metacarpal	Tumor 4 months	Curetted	Osteitis fibrosa with giant cell areas	Discharged well
36152	W. M. 11	Metatarsal	Tumor 6 months	Resected	Spindle cell variant predominated by giant cells	Discharged well
35104*	W. M.	Vertebra, 4th dorsal	Paralysis	Laminectomy	Spindle cell variant predominated by giant cells	Well 1 year
31657	W. M. 51	Metacarpal	Trauma 16 months	Amputation	Spindle cell variant predominated by giant cells	Well 6 years
29690	W. F. 31	Patella	Trauma 13 months	Curetted	Spindle cell variant predominated by giant cells	Well 6 years
27628*	.....	Metacarpal	Tumor	Excision	Cyst with giant cells	Well 7 years
27302	W. F. 4	Metacarpal	Tumor	Excision	Cyst with giant cells infected	Well 8 years
26953	W. F. 22	Hand, phalanx	Tumor 6 months	Amputation	Spindle cell variant with cysts and giant cells	Well 1 year
17049*	W. M. 20	Astragalus	Trauma 1 year	Curetted	Cyst with giant cells	Well 6 years
15597*	W. M.	Hand, phalanx	Tumor	Amputation	Cyst with giant cells	Discharged well
10524	W. M. 19	Metatarsal	Trauma 3 years	Amputation	Spindle cell variant predominated by giant cells	Discharged well
38484*	W. F.	Pelvis	Tumor 5 years	Explored	Osteitis fibrosa with giant cells	Well 1 year
34166	W. M. 51	Pelvis	Trauma 15 months	Curetted	Giant cells against cartilage	Well 5 years
29674	W. F. 38	Rib, 10th	Pain 6 years	Resected	Spindle cell variant predominated by giant cells	Well 4 years
28941	W. M. 22	Pelvis	Trauma 2 years	Curetted	Osteitis fibrosa with giant cell areas	Well 6 years
21580	W. M. 72	Clavicle	Fracture 50 years	Excision	Osteitis fibrosa with giant cell areas	Well 9 years
12378	W. F.	Pelvis	Pain 1 month	Excision	Osteitis fibrosa with giant cell areas	Well 18 years

* Sections were not seen by the authors.

tumor near the sacral region. With this exception, the other patients are well without signs of recurrence whereas in the typical giant cell tumor, there is about 20 per cent of recurrence following similar treatment.

This group of lesions raises the question as to why the giant cell tumor of the epiphysis fails to heal and is a progressive lesion, while a similar tumor in the small or flat bones progresses partially toward healing and the bone cyst arising in the metaphysis of the long bones presents a predominately healing reaction. The explanation lies in the differences in the anatomic structure of the bones involved. The epiphysis is to be associated with the giant cell tumor, the metaphysis with the bone cyst and the small or flat bones with the spindle cell variant of giant cell tumor. The epiphysis in which the typical giant cell tumor occurs lacks the defensive mechanism represented by the thick cortex of the metaphysis and diaphysis of the long bones and the overlying periosteum which as Macewen [23] and Poland [24] have pointed out, is equipped in the shaft and the metaphysis with a rich and vascular osteogenic layer which is lacking in the epiphysis after the age of 3 years. Hence, the giant cell tumor progresses in the epiphysis, whereas the bone destructive lesion in the metaphysis is reacted to effectively by the cortical bone in that region, and as the bone grows, the cyst or tumor area in the metaphysis is pushed toward the region of the midshaft within the protective confines of the thick cortical bone as a walled-off cavity (fig. 16). On the other hand, in the small bones, spacial limitations bring the developing tumor almost immediately into relation with cortical bone on all sides of the growth. An active defensive reaction against a giant cell tumor occurring in these bones is, therefore, set up early, and microscopically exhibits itself as a fibrous proliferation resulting in the so-called spindle cell variant. This early stimulation of compact bone on all sides of the lesion to produce fibro-ostosis makes it hard to find a region in a giant cell tumor of the small bones that is not invaded by young fibroblasts (figs. 26 *A* and *B* and 27 *A* and *B*). This tendency toward repair, however, although invoked early is not so marked as in the shaft of the long bones in which the cortex is thicker and more active.

The fact that lesions with characteristics of the giant cell tumor in small bones are often diagnosed as bone cysts demonstrates their healing tendencies. We feel, however, that the maintenance of two catagories for diagnosis of these lesions in the small bones is unjustified. For years cases showing this type of tumor in the small bones have been shifted back and forth, classified first with bone cysts and then with giant cell tumor or vice versa, two independent classifications being maintained for a single pathologic entity. It is clear that these lesions are giant cell tumors, showing a fair degree of healing reaction when

24. Poland, J.: Traumatic Separation of the Epiphyses, London, 1898.

they have the appearance of a spindle cell variant and a further degree of healing reaction when they appear as osteitis fibrosa with giant cell areas. Certainly they are not the mythical entity of a cyst in the small bones secondarily invaded by giant cells.

Dean Lewis [11] in his paper on "Giant Cell Tumor of the Vertebrae" approaches this point of view. In this contribution Lewis reviews seven-

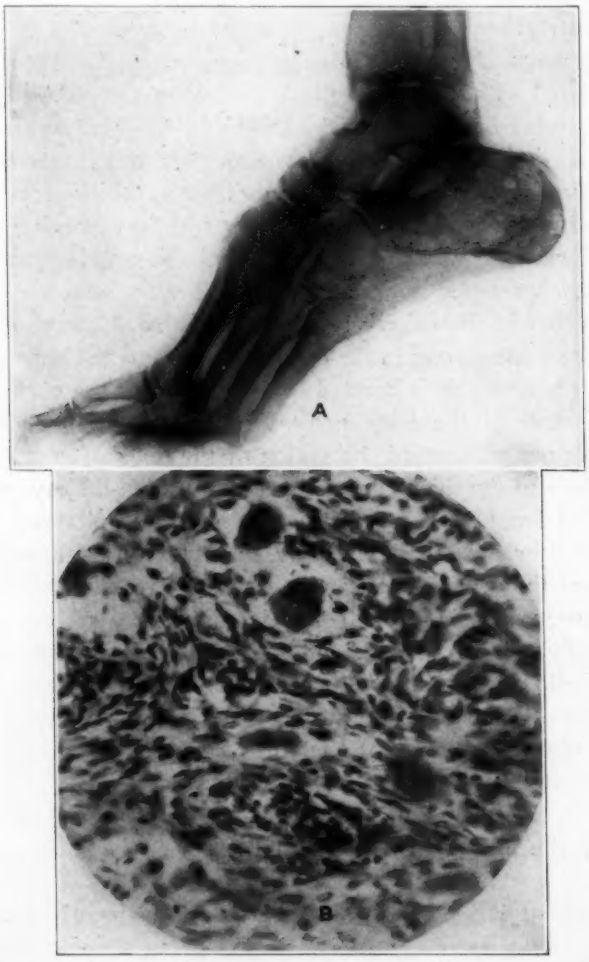

Fig. 26 (no. 17436).—Giant cell tumor in the os calcis. The x-ray picture, *A*, shows mottling and bone destruction. The shell of bone is intact. The microscopic structure, *B*, shows a spindle cell variant of the giant cell tumor.

teen cases including one of his own, pointing out that recovery after partial removal or exploration only, has been noted in thirteen of the seventeen cases, ossification occurring relatively frequently. In his series, the condition in two cases was located in the transverse processes of the lumbar vertebrae, two in the lamina of dorsal vertebrae and the

majority of the remainder (as far as can be determined from the case reports) in the lateral portions of the vertebral body next the lamina. As will be seen from figure 28 the site of these vertebral tumors in the region of compact bone and the early defensive reaction of fibro-ostosis produced, accounts for the healing emphasized by Lewis. Fortunately, sections from one of Lewis' cases are in the laboratory, and like the six of our own (fig. 29) the sections show spindle cell variation. Perforation and extension into neighboring bones occur more frequently in giant cell tumors of the spindle cell group (twelve of seventeen in Lewis' series), but this is only because they so frequently occur in small or flat bones in which the cortex is always thin and other bones are in close

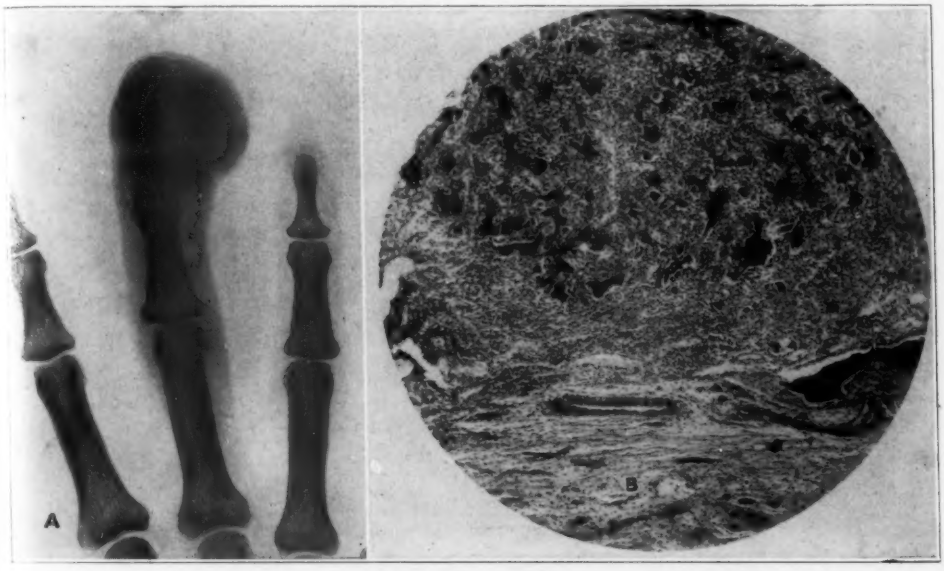

Fig. 27 (nos. 26953 and 17536).—The x-ray picture, *A*, shows a giant cell tumor of the terminal phalanx of the midfinger. There is involvement of both shaft and epiphysis in this small bone, and the tumor has perforated at the distal end. The photomicrograph, *B*, shows a giant cell tumor in the phalanx of a toe. Portions of trabeculae of cancellous bone are undergoing absorption, while the proliferation of fibroblasts in other areas shows a healing reaction.

approximation (fig. 30). Extension is not due to increased virulence of the tumor, as some pathologists claim who consider the spindle cell variant of the giant cell tumor a malignant form of this lesion (Ewing [7]).

From these studies the locality of the bone affected is seen to be an essential and determining factor in the pathologic process of giant cell tumor and the bone cyst. The epiphysis with its less active periosteum and thinner cortex allows the bone destructive giant cell tumor to

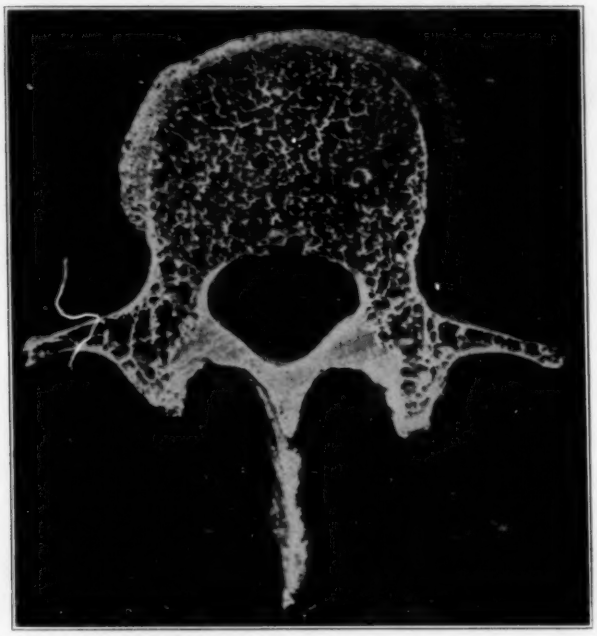

Fig. 28 (after Triepel-Breslau: Anat. Hefte **25**:209, 1904).—Cross-section of a lumbar vertebra showing the relation of cancellous to compact bone. As is explained in the text, the most frequent site of giant cell tumors is in the region of the laminae in the body, in the transverse process or in the lamina itself. This brings the tumor into contact with compact bone at an early stage.

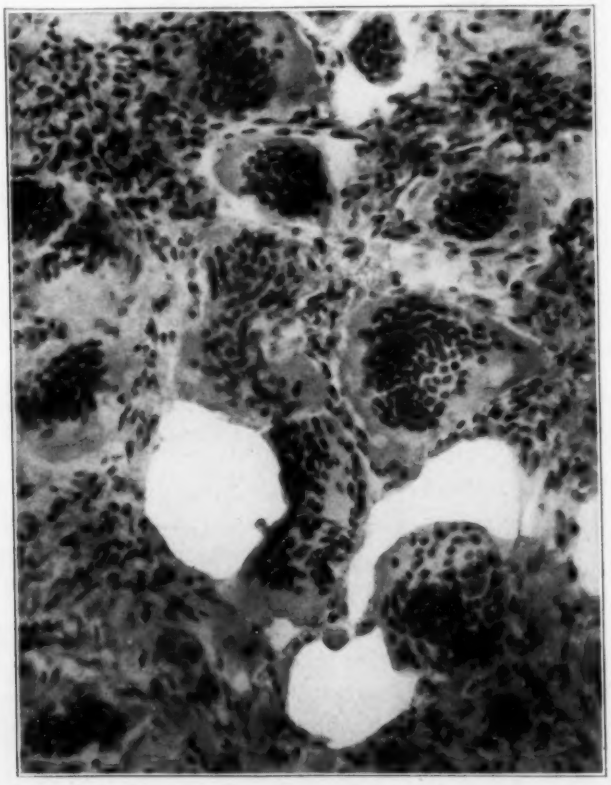

Fig. 29 (no. 38530).—Giant cell tumor of a vertebra. The giant cells are embedded in a stroma in which there are many spindle cells.

progress, while the thicker and more resistant cortex of the metaphysis, with its vascular subperiosteal layer promotes healing and makes for an arrested lesion, the bone cyst.

There is another factor of great importance, however, namely age. Bone growth and a bone cell with great proliferating potentialities are characteristic of youth. This power to heal a bone destructive lesion in the early years of life accounts for the fact that the arrested lesion, the bone cyst, is three times more frequent before the age of 20 than the

Fig. 30 (no. 24682).—Gross specimen showing the involvement of the third and fourth metacarpals by giant cell tumor. There is extension of the bone destructive process to several bones.

unhealed giant cell tumor (fig. 31). In fact, although several cases of bone cysts are recorded in this series in the epiphysis in patients under 5 years of age, giant cell lesions in any locality were not observed in patients under that age. The reason for this is that the vascular subperiosteal layer of the epiphysis does not begin to atrophy until after the age of about 3, and hence giant cell lesions arising in the epiphyses will be transformed into bone cysts at these earlier ages by the active periosteum.

Figure 31 emphasizes how the age period influences the physiologic factors underlying the differences between giant cell tumor and bone cyst. In this chart it will be seen that giant cell tumors do not occur until after the age of 5 when the periosteum of the epiphysis has lost much of its reparative powers. The healed bone cyst is the predominant lesion during the active growth period when the regenerative power of bone is at its height. To state it briefly, within certain age limits, as the healing powers of bone decline the frequency of the bone cyst decreases, while the frequency of the giant cell tumor increases.

Multiple Giant Cell Tumor and Multiple Osteitis Fibrosa.—A perusal of the contributions to this subject shows that a clinical and

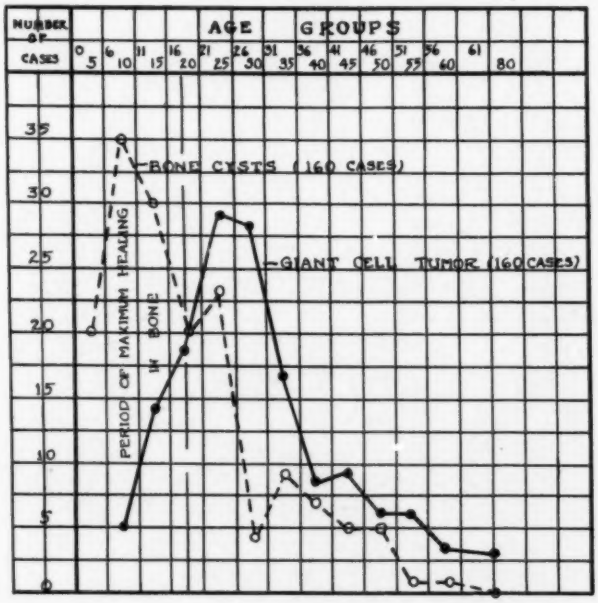

Fig. 31.—The age incidence of giant cell tumor compared with that of bone cysts. Within certain age limits (from 10 to 25) as the healing powers of bone decline, the frequency of bone cysts decreases while that of giant cell tumors increases.

pathologic overlap has long been recognized in this group of multiple tumors between bone cyst and giant cell tumors.[24a] Morton,[19] in reviewing the literature of multiple bone cysts, divides the lesions into group 1 without giant cell sarcoma and group 2 with giant cell sarcoma. In a similar manner, Alexander and Crawford[25] divide multiple giant cell

24a. Both Henderson (Minn. Med. **11**:542, 1928) and Meyerding (J. A. M. A. **83**:1323 (Oct. 25) 1924) recognized a relationship between these two tumors in their reports on solitary giant cell tumors.

25. Alexander, E. G., and Crawford, W. H.: Multiple Giant Cell Tumors, Ann. Surg. **86**:362 (Sept.) 1927.

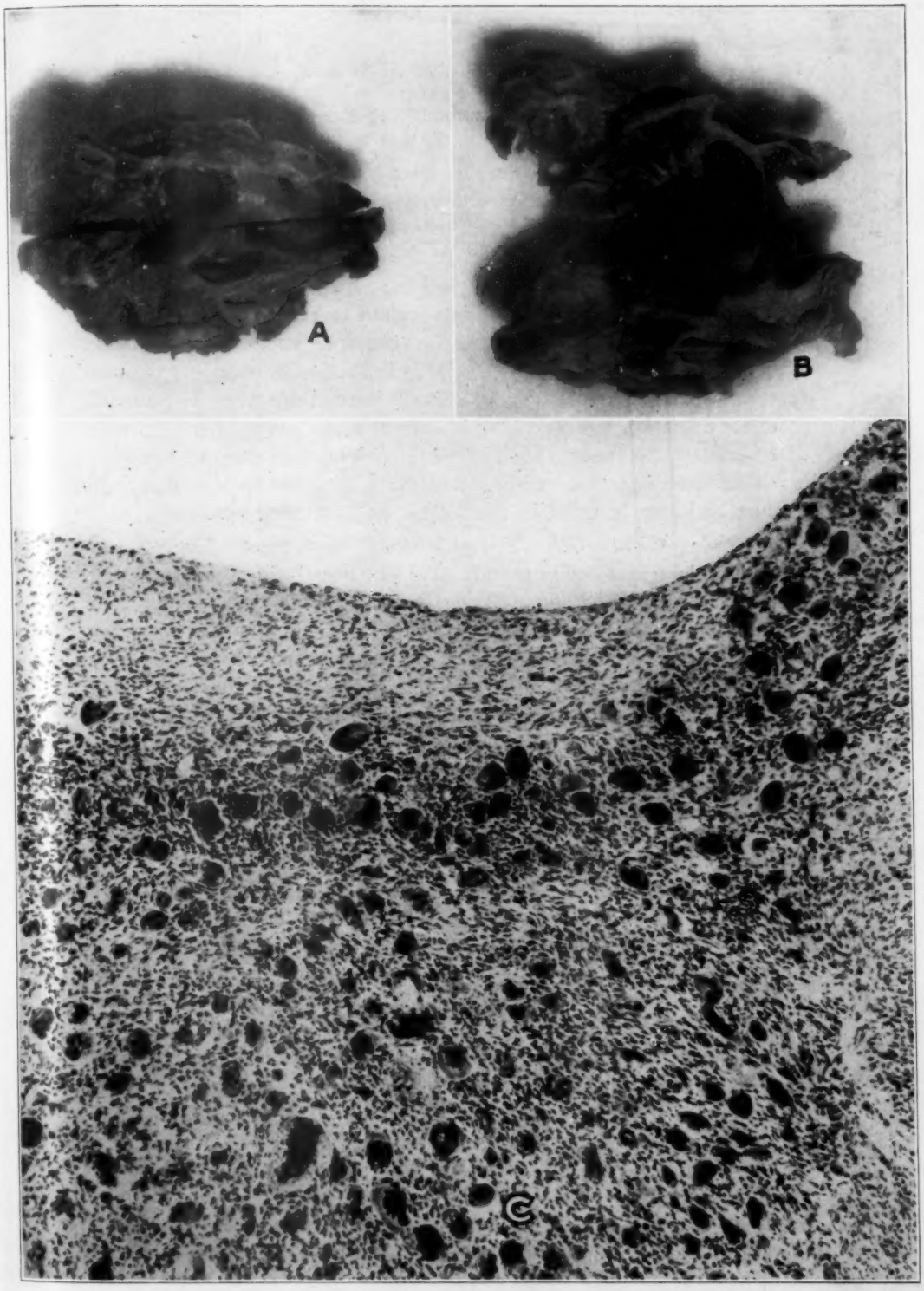

Fig. 32 (no. 37250).—Multiple giant cell tumors occurring in the tibia, radius, antrum and both humeri (gross and microscopic specimens from the same case). *A* and *B* are gross specimens showing the polycystic structure of the tumor; *C* is a photomicrograph showing the numerous large multinucleated giant cells occurring in a cyst wall.

tumors into two groups, those without and those with associated fibrocystic osteitis.

A review of our series of cases (table 8) emphasizes that in females past the age of puberty the condition predominates and that the males affected are usually under 13 and in these patients the condition is frequently associated with other juvenile diseases such as rickets, congenital syphilis, osteogenesis imperfecta and fragilitis ossium. Thus at the beginning of this discussion, it is important to realize that in cases of either multiple giant cell tumors or multiple bone cysts, there is frequently an associated disease, such as is not found in the single bone cysts and local giant cell tumors. Silver [12] implied this when he excluded from consideration in his article cysts occurring in seven different groups of associated diseases. This fact of a complicating disease, however, is not sufficiently emphasized in the reports on this group of tumors, and it must be borne in mind in the following discussion.

Multiple Giant Cell Tumor.—Many important features of the multiple giant cell tumor are illustrated in the following case (path. no. 37350, figs. 32 *A*, *B* and *C* and 33). The patient observed in 1922, was a white woman, aged 21, and the condition was of nine years' duration. The patient was well in 1928. The lesions were in the right tibia, the left radius and both humerii, all occurring just on the diaphyseal side of the epiphyseal line. In addition to this there was a tumor in the left antrum. The specimens illustrated were from the right tibia. In the gross the tumor was polycystic, and under the microscope even smaller cystic areas were present in large numbers. Giant cells predominated in the tissue about the cyst wall, and among these giant cells were numerous round cells. Elsewhere the stroma was composed of spindle cells and fibroblasts and further out there were islands of new bone and typical osteitis fibrosa. There was much hemorrhage in the tissue, and some small cysts were occupied by blood.

There were too many giant cells in the sections for the tumors to be classed as simple cysts. Similarly, we have never observed a case of typical bone cyst in the upper jaw. Yet, the tumors in the long bones are all on the shaft side of the epiphysis, and the patient was only 15 years of age when these lesions first appeared. These two facts and the polycystic nature of the tumor favor osteitis fibrosa, and the sections show numerous areas to this tissue. How is a combination of giant cell tumor and bone cyst to be explained in the same case?

Usually, the single bone cyst is an arrested lesion as we have shown, an arrested giant cell tumor. When it is multiple, and particularly when it is polycystic, we have reason to believe that the general rule has been broken and that the lesion has become progressive. In the above case

TABLE 6.—[illegible]

Path. No.	Race, sex, Age	Location	Symptoms	X-ray	Treatment	Microscopic	Associated Disease	Results
27258	W. M. 12	Upper humerus, lower radius, upper fibula, upper femur	Trauma	Cystic expansion	No operation	No note	Osteogenesis imperfecta	Well ten [illegible] years
9982	W. F. 64	Fibula, tibia, os calcis	Deformity 3½ years	Cyst, fracture, bending	Excision	No note	Osteogenesis imperfecta	Deformity still persists
30290	W. M. 18	Skull, femora, sacrum	Marasmus	Areas of absorption	Explored	No note	Rickets	Unimproved
32070	W. F. 16	Humerus, radius	Dysfunction 10 months	Cystic perforation	Untreated	Cysts with areas of giant cells	Not determined	Well ten [illegible] years
27250	W. F. 21	Humeri, radius, tibia, upper jaw	Tumor 3 years	No note	Untreated	Cysts with areas of osteitis fibrosa and giant cells	Not determined	Well 3 years
33372	W. F. 22	Vertebra, pelvis femur, tibia	Trauma 8 months	No note	Untreated	Cysts with areas of osteitis fibrosa and giant cells	Not determined	Discharged unproved
33358	W. M. 34	Tibia, humerus, radius	Trauma 3 years	No note	Untreated	Cysts with areas of osteitis fibrosa and giant cells	Osteomalacia	Unimproved 3 years later
33151	W. M. 38	Fibula, tibia	Trauma 1 month	Cyst with fracture	No note	No note	Not determined	Discharged well
27278	W. F. 15	Tibia, multiple	No note	Cystic bending	Explored	Cysts with areas of giant cells	Rickets	Discharged unproved
31689	W. F. 25	Fibula, tibia, femur	Fracture 3½ years	Cystic with fracture	No note	Cysts with areas of osteitis fibrosa	Osteogenesis imperfecta	Discharged unproved
26916	W. F. 32	Scapula, sacrum, humerus	Trauma 2 years	No note	No operation, x-ray	No note	Not determined	Well 7 years
29849	W. F. 14	Radius, ulna, femur, tibia, fibula	Deformity 7 years	Cystic with infection	No note	No note	Rickets	Discharged unproved
28846	W. F. 2	Jaws, pelvis	Tumor 7 months	No note	Untreated	Cysts with areas of osteitis fibrosa and giant cells	Syphilis, congenital	Discharged unproved
28074	W. F. 15	Femora, tibia	Deformity 13 years	Cystic bending	Untreated	Cysts with areas of giant cells	Osteogenesis imperfecta	Discharged unproved
27785	W. F. 45	Humerus, ilium, ribs	Fracture 3 years	Shaft of humerus destroyed	No note	No note	No note	Well 7 years
28893	W. F. 44	Tibia, ilium, femur	Fracture	No note	Resected	Cysts with areas of osteitis fibrosa and giant cells	Osteomalacia	Died of other causes
28891	W. F. 3	Tibia, patella, radius, ulna, humerus	Tumor 10 months	No note	Untreated	No note	Multiple periostitis	Discharged unproved
28890	W. F. 55	Humerus, tibia	Pain	Cystic bending of spine	Excision	No note	Osteomalacia	Discharged unproved
22217	W. F. 15	Femur, multiple	Pain and deformity 6 years	Bending, infection	Osteotomy	Areas of osteitis fibrosa	Fragilitas ossium	Recurrence
16823	W. F. 21	Radius, humerus	Pain 2 years	Cystic, encapsulated	Untreated	No note	Undetermined	Well 2 years

tumors into two groups, those without and those with associated fibrocystic osteitis.

A review of our series of cases (table 8) emphasizes that in females past the age of puberty the condition predominates and that the males affected are usually under 12 and in these patients the condition is frequently associated with other juvenile diseases such as rickets, congenital syphilis, osteogenesis imperfecta and fragilitis ossium. Thus at the beginning of this discussion, it is important to realize that in cases of either multiple giant cell tumors or multiple bone cysts, there is frequently an associated disease, such as is not found in the single bone cysts and local giant cell tumors. Silver [15] implied this when he excluded from consideration in his article cysts occurring in seven different groups of associated diseases. This fact of a complicating disease, however, is not sufficiently emphasized in the reports on this group of tumors, and it must be borne in mind in the following discussion.

Multiple Giant Cell Tumor.—Many important features of the multiple giant cell tumor are illustrated in the following case (path. no. 37250, figs. 32 *A, B* and *C* and 33). The patient observed in 1922, was a white woman, aged 21, and the condition was of nine years' duration. The patient was well in 1928. The lesions were in the right tibia, the left radius and both humerii, all occurring just on the diaphyseal side of the epiphyseal line. In addition to this there was a tumor in the left antrum. The specimens illustrated were from the right tibia. In the gross the tumor was polycystic, and under the microscope even smaller cystic areas were present in large numbers. Giant cells predominated in the tissue about the cyst wall, and among these giant cells were numerous round cells. Elsewhere the stroma was composed of spindle cells and fibroblasts and further out there were islands of new bone and typical osteitis fibrosa. There was much hemorrhage in the tissue, and some small cysts were occupied by blood.

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TABLE 8.—*Multiple Giant Cell Tumor and Bone Cyst*

Path. No.	Race, Sex, Age	Location	Symptoms	X-Ray	Treatment	Microscopic	Associated Disease	Results
37258	W. M. 12	Upper humerus, lower radius, upper fibula, upper femur	Trauma	Cystic expansion	No operation	No note	Osteogenesis imperfecta	Well less than 5 years
36682	W. F. 4	Fibula, tibia, os calsis	Deformity 3½ years	Cyst, fracture, bending	Excision	No note	Osteogenesis imperfecta	Deformity still persists
36206	W. M. 3	Skull, femora, sacrum	Marasmus	Areas of absorption	Explored	No note	Rickets	Unimproved
35702	W. F. 16	Humerus, radius	Dysfunction 10 months	Cystic perforation	Curetted	Cysts with areas of giant cells	Not determined	Well less than 5 years
37250	W. F. 21	Humeri, radius, tibia, upper jaw	Tumor 3 years	No note	Curetted	Cysts with areas of osteitis fibrosa and giant cells	Not determined	Well 3 years
33572	W. F. 22	Vertebra, pelvis femur, tibia	Trauma 8 months	No note	Curetted	Cysts with areas of osteitis fibrosa and giant cells	Not determined	Discharged improved
33358	W. M. 34	Tibia, humerus, radius	Trauma 3 years	No note	Curetted	Cysts with areas of osteitis fibrosa and giant cells	Osteomalacia	Unimproved 3 years later
33151	W. M. 18	Fibula, tibia	Trauma 1 month	Cyst with fracture	No note	No note	Not determined	Discharged well
32732	W. F. 5	Tibia, multiple	No note	Cystic bending	Explored	Cysts with areas of giant cells	Rickets	Discharged improved
31889	W. F. 25	Fibula, tibia, femur	Fracture 3½ years	Cystic with fracture	No note	Cysts with areas of osteitis fibrosa	Osteogenesis imperfecta	Discharged improved
30316	W. F. 52	Scapula, sacrum, humerus	Trauma 2 years	No note	No operation, x-ray	No note	Not determined	Well 7 years
29849	W. F. 14	Radius, ulna, femur, tibia, fibula	Deformity 7 years	Cystic with rarefaction	No note	No note	Rickets	Discharged improved
28946	W. F. 23	Jaws, pelvis	Tumor 7 months	No note	Curetted	Cysts with areas of osteitis fibrosa and giant cells	Syphilis, congenital	Discharged improved
28074	W. F. 15	Femora, tibia	Deformity 12 years	Cystic bending	Curetted	Cysts with areas of giant cells	Osteogenesis imperfecta	Discharged improved
26785	W. F. 45	Humerus, ilium, ribs	Fracture 3 years	Shaft of humerus destroyed	No note	No note	No note	Well 7 years
25893	W. F. 44	Tibia, ilium, femur	Fracture	No note	Resected	Cysts with areas of osteitis fibrosa and giant cells	Osteomalacia	Died of other causes
25891	W. F. 33	Tibia, patella, radius, ulna, humerus	Tumor 6 months	No note	Curetted	No note	Multiple periostitis	Discharged improved
25890	W. F. 55	Humerus, tibia	Pain	Cystic bending of spine	Excision	No note	Osteomalacia	Discharged improved
25247	W. F. 15	Femur, multiple	Pain and deformity 6 years	Bending, rarefaction	Osteotomy	Areas of osteitis fibrosa	Fragilitis ossium	Recurrence
10523	W. F. 21	Radius, humerus	Pain 2 years	Cystic, encapsulated	Curetted	No note	Undetermined	Well 29 years

the age of onset and the location of the tumors in the metaphysis of the long bones would seem to indicate that had this tumor become arrested, it would have been a typical bone cyst. Instead it had become progressive, showed multiple bone involvement, polycystic structure and a predominance of giant cells, the expected explanation for this failure to be arrested being that there was an associated disease in the skeleton that prevented the usual protective overgrowth of fibro-ostosis from taking place.[25a] When we review all the multiple cases in the literature, and those in our collection, we are impressed with two facts, that the patients are either females at the age during which osteomalacia occurs or males and young girls at the age in which juvenile bone diseases are common. The associated skeletal diseases vary, but some complicating factor is usually present (fig. 34 *A* and *B*) such as osteogenesis imperfecta, rickets, congenital syphilis, fragilitis ossium and osteomalacia.

From the facts already mentioned, the conclusions follow that most multiple giant cell tumors would, without a complicating factor, develop clinically into a bone cyst and that their failure to become so arrested and the persistence of giant cell areas in them indicate a progressive lesion. The giant cells present indicate the more primitive and original structures of these lesions, and ordinarily they disappear from the healing solitary bone cysts by the time that the lesion comes under observation. These multiple giant cell tumors, therefore, throw considerable light on the earlier stages of osteitis fibrosa.

Multiple Bone Cysts.—A review of multiple bone cysts in the literature and in our own series emphasizes the fact that the lesions described under this head represent a conglomeration of pathologic entities.

25a. Although in this case we had at our disposal only the history, x-rays and microscopic material, and although we were unable to verify the conclusion by metabolic studies, the fundamental conception advanced here has been recently confirmed by evidence placed at our disposal through the courtesy of Dr. R. M. Wilder of the Medical Division of the Mayo Clinic. The case, that of a white woman, aged 32, studied by him over a period of four years (to be reported in *Endocrinology*) duplicates in its essential clinical features the one already outlined, and in addition shows abnormal calcium and phosphorus values in the blood serum which ultimately proved dependent on a hyperparathyroidism associated with a benign adenomatous tumor of the parathyroid gland. Giant cell tumors occurred in the lower part of the femur, the upper jaw and at the site of the right lower bicuspid (epulis). The serum calcium was elevated to 11.4 mg. per hundred cubic centimeters, and the phosphorus lowered to 1.4 mg. per hundred cubic centimeters. As a result of this removal of lime salts from the bones, the pelvis showed rarefaction and distortion similar to osteomalacia and the skull and spine areas of absorption. Improvement followed removal of the parathyroid tumor, a diet high in vitamins and ultraviolet light therapy. The serum calcium had returned to 8.3 mg. per hundred cubic centimeters and the phosphorus to 1.8 mg. per hundred cubic centimeters when the patient was last examined in April, 1929.

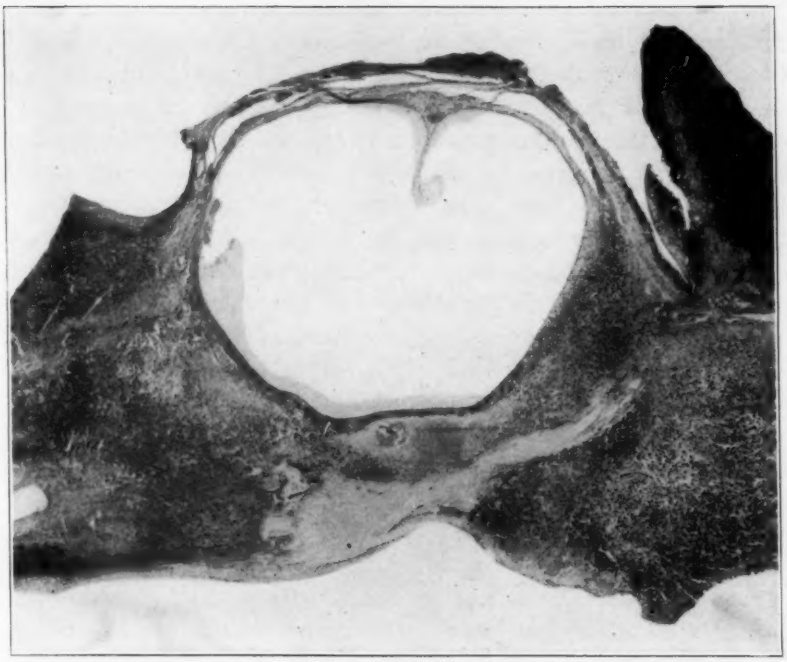

Fig. 33 (no. 37250).—Low magnification of the cyst shown partially in figure 32 *C*. The numerous black dots in the tissue are seen to be giant cells under higher magnification. The broken septum dangling from the roof of the cyst shows that the fusion of two minute cysts has occurred.

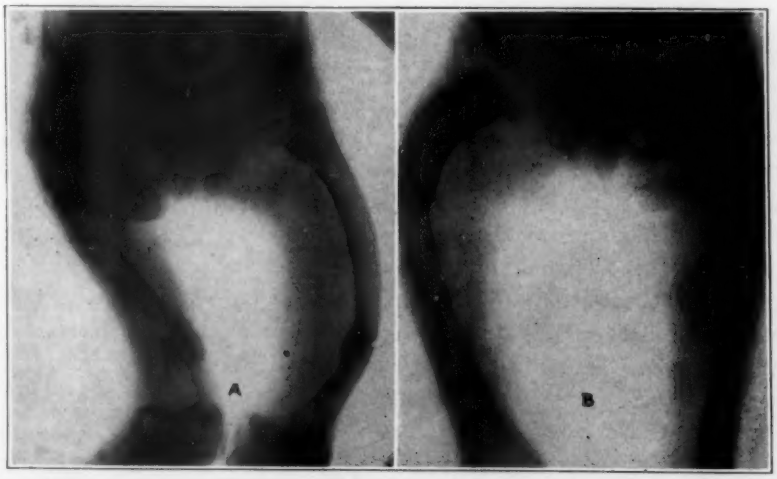

Fig. 34 (nos. 25247 and 28074).—Two cases showing associated skeletal disease with multiple bone cysts and multiple giant cell areas. The bending of the bones and the pathologic fractures are associated with fragilitis ossium (*A*) and osteogenesis imperfecta (*B*).

When selected on a microscopic basis, these lesions show under the microscope a predominance of osteitis fibrosa, fewer, but some giant cells, and less of the polycystic structure. Clinically, this group is to be distinguished from multiple giant cell tumors by the higher age limits and the longer duration of the symptoms. This is what would be expected if multiple bone cysts represented a later stage in the same pathologic process as multiple giant cell tumors. When outspoken cases of Paget's osteitis deformans, osteomalacia, osteoarthritis and similar diseases are excluded, all the evidence is found to support this view. When the cysts were large and the tissue sparse in giant cells, we found the average age of the patients to be higher and the duration of the symptoms to be longer (table 8). Ultimate healing without surgical intervention occurs in multiple bone cysts, the process responsible for the multiplicity of the lesion apparently subsiding, although the cysts themselves may remain many years as latent lesions. In such cases it will not be possible to find an associated disease when these lesions come under observation at a late date.

In passing it is well to note here certain observations made in this group of multiple bone tumors. In the majority of the twenty cases in this series studied in this laboratory the urine was examined for Bence Jones bodies. In all cases the results of the examination were negative, an interesting diagnostic point in view of the frequency of Bence Jones bodies in the urine of patients with multiple myeloma (65 per cent), and the association of these bodies with other multiple bone tumors (Geschickter and Copeland [26]).

THE NATURE OF THE GIANT CELL

It has been pointed out that the giant cell tumor under the microscope shows a typical structure characterized by many large giant cells embedded in a round cell stroma. The spindle cell variant of this histologic picture and indeed, the microscopic structure of osteitis fibrosa and its variants were shown to be due to a healing reaction or fibro-ostosis in most instances superimposed on the original giant cell picture. In this way and also by pointing out transitional lesions, it was shown that these various forms of disease of the bone in all probability originate from a single underlying pathologic process characterized histologically by the proliferation of giant cells. A fundamental importance, therefore, attaches to the elucidation of the nature of the giant cell and the causes for its proliferation.

In contrast to the bone formative tissue of fibro-ostosis, giant cell areas in the skeleton are associated with bone destruction. This is well

26. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:807 (April) 1928.

illustrated by figure 35 which shows a bone spicule lying at the margin of a giant cell tumor occurring in the lower epiphysis of the femur. At one end, the spicule is enlarged and club-shaped and in contact with it are numerous osteoblasts applied to its surface. Surrounding this enlarged end, beyond the osteoblasts, are numerous spindle cells and fibroblasts. At this end there is little doubt that new bone formation is taking place. At the other end the spicule is narrower, and the margins are frayed and worm eaten in appearance. Near at hand are giant cells

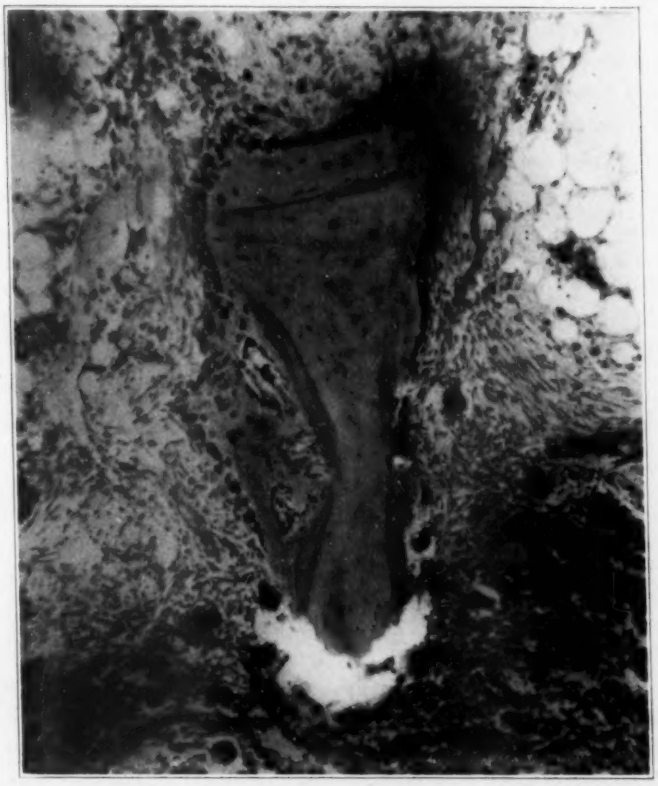

Fig. 35 (no. 3623).—A bone spicule from the margin of a giant cell tumor in the lower end of the femur. At the large end of the spicule, osteoblasts embedded in fibrous tissue are laying down new bone. At the small tumor margin of the spicule, the frayed and worn edges indicate bone destruction. Both the bone destructive nature of giant cell tumor and the healing reaction of fibro-ostosis are illustrated by this section.

embedded in a round cell stroma. The histologic picture at this end of the spicule is that of typical giant cell tumor, and it is plainly evident that bone destruction is occurring here.

Varieties.—The question arises whether the giant cells in the tumor are responsible for this bone destruction and if the tumor process repre-

sents a proliferation of osteoclasts as pointed out by Stewart of Leeds.[4] Much work has been expended in an endeavor to determine whether the giant cell erodes bone. The question has not been conclusively settled, although a well defined distinction has been drawn between giant cells of the hemopoietic series, giant cells in malignant tumors with rapid mitoses, and foreign body giant cells. The so-called osteoclast or giant cell of the epulis type found in giant cell tumor is undoubtedly related to the foreign body type. It represents a formation of cells characteristic of a phagocytic process, and as Lewis [27] has shown, these larger elements are formed by the fusion of smaller cells, with occasionally a further multiplication of nuclei by mitotic division. Giant cells of this phagocytic type are found when agar-agar is introduced into muscle, about foreign bodies introduced into wounds, about gummas and tubercules, epithelial pearls in squamous cell carcinoma and about necrotic fibrous tissue in other tumors. The presence of these cells in such a miscellaneous group of lesions is probably to be explained on a basis of a chemotaxis to a collagen-like substance present in all of these conditions. It is important to recall in this connection that Leriche and Policard [22a] have recently shown that a collagenous matrix is fundamental to the formation of all bony substances.

But though related to the foreign body type in formation and phagocytic nature, the giant cell of giant cell tumor with its typical retinue of round cells is by no means to be confused with the foreign body giant cell embedded in granulation tissue. No particular histologic training is necessary to distinguish between these two types of tissue, and the current tendency to regard giant cell tissue everywhere as granulation tissue and to interpret all tumors of this form on such a basis is unjustifiable despite the contentions of Mallory,[28] Konjetzny [20] and many others.

Histologically the giant cell in granulation tissue is a smaller cell, with fewer nuclei, peripherally rather than centrally placed. The surrounding round cells are leukocytes of various types and are relatively small. The giant cells although clumped rarely average as many as 10 or 15 cells to a low powered field. In typical giant cell tumor tissue the giant cells are larger, have more nuclei (from 15 to 200) centrally placed and average over 30 to the low powered field. The accompanying round cells are not of the infectious leukocytic type but are larger, more uniform in size and structure, and their nuclei correspond in morphology to the nuclei of the giant cells.

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27. Lewis, W. H.: Mononuclear Blood Cells, The Harvey Lectures, 1925-1926, series 21, p. 83.

28. Mallory, F. B.: Giant Cell Sarcoma, J. M. Research **74**:463, 1911.

Fundamentally there is a difference, and while recognizing the giant cell of the epulis type as related to the foreign body series, we view it as a specialized form and propose to demonstrate the osteoclastic nature of all giant cell tumors and their inherent relation to bone even when occurring in the soft parts.

Such a view of the osteoclastic giant cells interprets them as phagocytic elements which exhibit the property of giant cell formation when bone or calcified cartilage is being resorbed. The question of whether the giant cells directly or indirectly, mechanically or chemically are accomplishing the bone destruction is irrelevant to this discussion. Suffice it to say, that they are an early manifestation rather than an end-product of bone destruction as claimed by Arey,[29] and they may be taken as an index that the process is active, since when this type of tissue proliferates the process increases. Embryologic studies emphasize this point.

The Relation of the Histogenesis of Intracartilaginous Ossification to Giant Cell Tumor.—Although works on embryology since 1890 (Quain[30]) give the histogenesis of the long bones in some detail, the importance of this process for giant cell tumor made a reconsideration of the whole process essential. For this purpose we were fortunate in having the privilege of studying a most valuable collection of human embryos in the Carnegie Institute of embryology placed at our disposal through the courtesy of Professor Streeter, director of the institute.

In the long bones, the process of osteogenesis is similar in both the shaft and the epiphysis, the two being formed by intracartilaginous ossification. There are usually three centers of ossification, one for the diaphysis and one for each epiphysis. The center of ossification of the shaft develops first, new bone extending in two directions toward each metaphysis. The two epiphyseal centers develop much later (fig. 36). Hence, the areas in which new bone formation persists in the child and the young adult are in the metaphysis of the bones on the shaft side of the epiphyseal line and in the epiphysis. As we have seen, these persisting centers of ossification are the sites of the lesions of bone cysts and giant cell tumor. The histologic processes going on in these regions or centers explain how these growths arise.

The new bone is preformed in cartilage and later replaced by permanent bone. This process may be said to take place by transformations occurring in three stages: (1) the calcification of cartilage to form primary areolae; (2) the invasion and resorption of the areolae and

29. Arey, L. B.: Origin and Fate of Osteoclasts, Am. J. Anat. **26**:315, 1919-1920.

30. Schafer, E. A., and Thane, G. D.: Quain's Elements of Anatomy, ed. 10, 1891, vol. 1, part 2, pp. 268-284.

their walls; (3) the laying down of permanent perichondral bone. Both longitudinal and transverse sections are necessary to a clear conception of these three stages, and both are illustrated here (figs. 36 to 41). In the longitudinal sections the ends of the bone are still primitive cartilage. Toward the center of the shaft, the cartilage cells line up in rows, enlarge and secrete an increased hyalin matrix which becomes calcified to form a honey-combed arrangement. The cartilage cells within these calcified

Fig. 36 (no. 40936).—The femur of a monkey fetus at term. The photograph illustrates the persistence of cartilage in the epiphysis and the formation of new bone in the metaphysis. The marrow cavity is not yet fully formed.

compartments next shrivel and atrophy, their nutrition being cut off by the calcified walls which form the primary areolae. All this occurs in the regions that are the future medullary cavity. In the subperichondral region (what is to be subperiosteal) along the margins of the shaft, osteoid tissue is being laid down by the perichondrium. In the next stage, this perichondral osteoid tissue is perforated by blood vessels that proceed inwardly to the primary areolae (fig. 40 *A* and *B*).

This stage in which the calcified areolae are invaded by blood vessels and resorbed is the most significant phase for the understanding of giant cell tumor and is best seen in cross-sections taken from the long bones of young human embryos. It is just this phase that is most poorly described in the textbooks, and the cross-sections illustrated here are usually omitted. In the transverse sections it will be seen that the primary areolae are invaded and resorbed by buds of tissue proceeding from the outlying mesenchyme surrounding the perichondral bone. The manner in which these buds perforate the perichondral bone, invade the calcified areolae and absorb them is most important. Mesenchymal cells

Fig. 37 (no. 40936).—Photomicrograph of the epiphyseal line of the femur shown in figure 36. Cartilage has calcified to form the primary areolae. Giant cells or osteoclasts are eating their way into the calcified cartilage followed by small vessels, preliminary to the formation of permanent bone. Cells of the newly formed marrow cavity are seen at the bottom of the picture.

concentrate, their nuclei darken and the cells agglutinate to form giant cells or osteoclasts. These giant cells are first to perforate the perichondral bone (fig. 41) and the first to force entrance into the compartments of the calcified areolae (figs. 37 and 38). In their wake come newly formed capillaries, osteoblasts and other mesenchymal elements. When the stage of resorption of calcified cartilage is at its height, and the medullary cavity is being formed, a cross-section of a young bone in an embryo of from 90 to 100 mm., taken from this region, will show a

veritable giant cell tumor. The cavity of the bone will be filled with giant cells, round cells, small blood vessels, hemorrhage and osteoblasts. Later the osteoblasts persist near the margin of the medullary cavity to aid in the formation of cancellous and then compact bone, while the marrow cavity itself becomes filled with young bone marrow elements.

These embryologic studies emphasize the association of the giant cells with the perforation of new perichondral bone and the resorption of calcified cartilage. The specimens show clearly that the giant cell

Fig. 38 (no. 40936).—Higher magnification of the same area shown in figure 37. Three primary areolae formed by calcified cartilage with a portion of two others are shown in the photomicrograph. One areola is still intact, and in it two degenerating nuclei of cartilage cells are seen. In the other areolae giant cells are seen forcing their entrance through calcified cartilage. Note that the nuclei of the giant cells are entirely different in morphology from those of the degenerated cartilage cells, and that they outnumber the cells in the calcified area. This disproves the statement of Arey that giant cells are rarely seen when calcified cartilage is undergoing resorption and that the giant cells are formed as a by-product of degenerated dissolving bone by the agglutination of the nuclei of old bone cells.

proceeds inwardly from outside of the shaft of the bone and that these multinucleated elements may arise in the primitive periosteal tissue. It is not necessary to presume that they arise from the marrow reticulum as many histologists believe (Maximow [31]) nor that they are derived from the endothelium of capillaries. The only distinct evidence is in favor of the view that they are formed from primitive mesenchyme and that such mesenchyme exists periosteally.

Giant cell formation, therefore, marks the beginning of bone perforation in the embryo, and in the wake of these cells new blood vessels and osteoblasts follow. Over and over again in both giant cell tumor and osteitis fibrosa, particularly of the polycystic variety, we have observed giant cells on the outward borders of new blood vessels and vascular spaces (figs. 5, 45 and 57) showing that the giant cells in these lesions retain the same histologic function as the osteoclasts seen in human and other mammalian embryos.[31a]

Other points of interest in the embryologic processes of bone are the formation of perichondral osteoid tissue directly from the mesenchymal osteoblasts without the medium of cartilage which parallels exactly the bone formation described in this paper as fibro-ostosis, and the resemblance of calcified cartilage in the embryo to analogous tissue seen in osteogenic sarcoma.

Turning now to the consideration of giant cell tumors, the location of these lesions (and also the healing form of bone cysts) at the sites and at the ages when intracartilaginous bone is being formed relates them to this process. More specifically and convincingly the bone destructive character of these lesions and the prevalence of giant cells or osteoclasts in them relates them to the process of resorption of temporary bone characterized by the proliferation of osteoclasts or giant cells which has been described in the foregoing review of histogenesis in the long bones. From this we conclude that the giant cell tumor and the related lesion of bone cyst are the result of an abnormal hyperplasia of osteoclasts preceded by a normal stage in which osteoclastic proliferation is taking place as a phase in the histogenesis of intracartilaginous bone. From this point of view, the term progressive osteoclastasia is suggested for the process underlying the giant cell tumor and the term

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31. Maximow, A.: Untersuchungen über Blut und Bindegewebe, Arch. f. mikr. Anat. **76**:1, 1910.

31a. That this same histologic function of the osteoclasts as forerunners of the vascularization and resorption of temporary calcified structures holds for repair processes and even for foreign bodies is shown by the experiments of Pollock and others on the viability of transplanted bone (Arch. Surg. **18**:607 [Feb.] 1929). Here in experimental bone transplants it was found that giant cells attacked the transplanted bone preliminary to its vascularization and the formation of new bone.

regressive osteoclastasia for bone cysts. These terms show their relationships one to the other and also to the normal process of osteoclastic proliferation that goes on in the histogenesis of the long bones.

GIANT CELL TUMORS OF THE SKULL

The validity of the hypothesis which relates giant cell tumor to the resorption of temporary bone or calcified cartilage is to be proved by the elucidation and the prediction of the facts in regard to these tumors wherever they are found. So far as giant cell tumors and bone cysts in the long bones are concerned, this conception holds, for by age incidence,

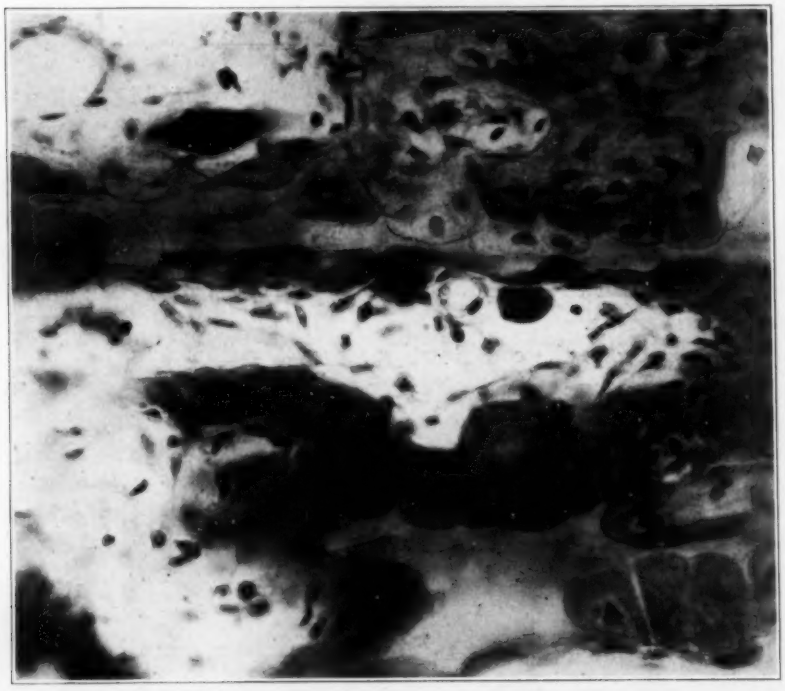

Fig. 39 (no. 40978).—High power field of an epiphysis of a child 11 months old showing calcified cartilage attacked by giant cells. This shows a similar process which is more clearly illustrated in figures 37 and 38.

location and histologic structure these lesions are related to osteogenesis via cartilage. However, tumors of the giant cell variety occurring in the skull, along the alveolar border in the form of the giant cell epulis, and in tendon sheaths and soft parts offer greater difficulties in the establishment of this relationship to the resorption of temporary bone. To predict such a relationship for giant cell tissue in this diversity of lesions is to bring the conception of giant cell tumor thus far advanced to a crucial test. In order to carry out this test these various types of lesions will now be examined in detail.

The Chondrocranium in Relation to Giant Cell Tumors of the Skull.—If the intimate association of the pathologic changes in giant cell lesions to the resorptive process in cartilaginous bone is a fact, then the bones of the skull and face should furnish valuable evidence to support it. For it is known that certain bones of the cranium—particularly the frontal, parietal and tabular portion of the occipital—which compose

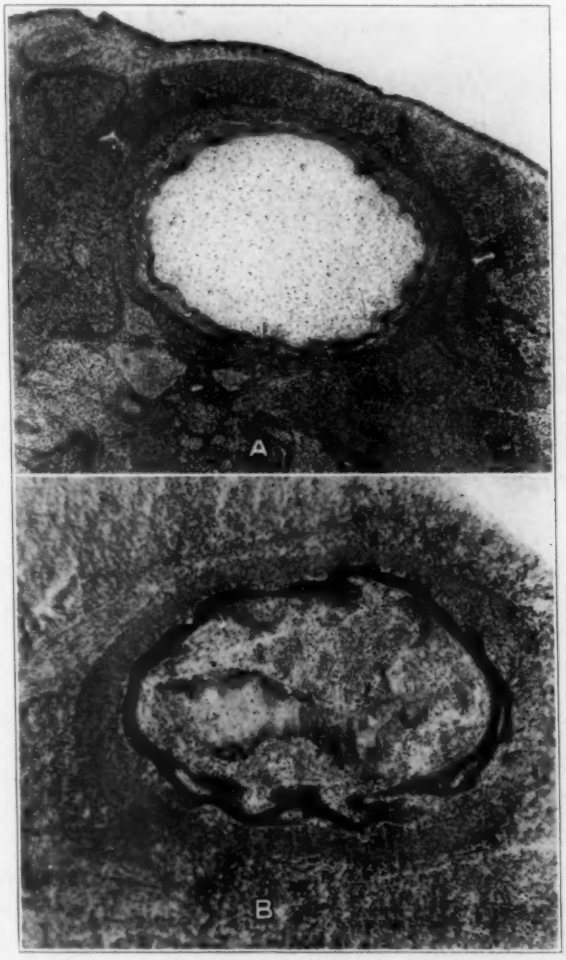

Fig. 40 (no. 40934).—Cross-sections of the humerus of a human embryo of 90 mm. The upper section, *A*, shows the perforation of the perichondral osteoid tissue by mesenchymal elements at numerous points proceeding inwardly from the primitive periosteum. The calcified cartilage is about to undergo resorption by these invading mesenchymal elements. *B* is a section near the region of the midshaft of the same bone, showing a more advanced stage in the resorption of calcified cartilage by mesenchymal elements and the formation of the marrow cavity. Note how the subperichondral osteoid tissue has been broken through at different points. (Sections furnished through the courtesy of Dr. Streeter of the Carnegie Institute of Embryology.)

the calvarium are formed from membrane rather than cartilage, as are most of the bones of the face. These bones should be immune to direct involvement by either osteitis fibrosa or giant cell tumor. It is true that they are provided with periosteum and that this tissue retains osteoclastic as well as osteoblastic potentialities, but in such instances, the lesion should be periosteal instead of central and present other peculiarities. A review, therefore, of the exact histology and location of giant cell tumors of the head becomes of special significance.

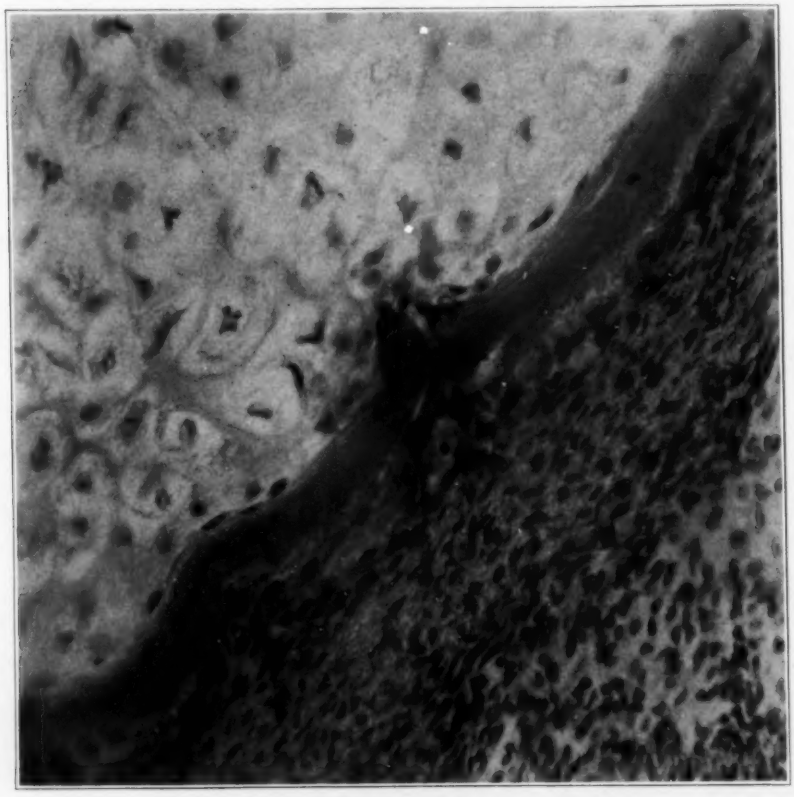

Fig. 41 (no. 40934).—Higher magnification of the section shown in figure 40 *A*. The photomicrograph illustrates the first step in the resorption of calcified cartilage. A giant cell proceeding from the primitive periosteum is perforating the perichondral osteoid tissue and attacking the primary areola. In its wake is shown a small blood vessel and other mesenchymal elements arising from the primitive periosteum. The picture disproves the assumption by numerous embryologists that the giant cells of an osteoclastic nature are formed from the reticulum in the marrow cavity, for here we see that the giant cell is entering the future marrow cavity from the periosteum outside of the bone.

Excluding the epulis of the alveolar border the records of the surgical pathologic laboratory of the Johns Hopkins Hospital extending over a period of thirty-five years show only twenty-two cases of giant cell

tumor occurring in the head. Bone cysts did not occur in this locality. Two of the giant cell tumors were found in the temporal fossa, six are recorded for the upper jaw and fourteen in the lower jaw. In the purely membranous portion of the calvarium (the frontal and parietal bones), not a single instance of these lesions is recorded (tables 10 and 11). The three sites of the lesions, the temporal fossa, the upper jaw and the mandible, it is true, are in regions of membranous bone. The squamous portion of the temporal bone, the superior maxillae and a large portion of the mandible are formed from membrane. But there are also cartilaginous centers of ossification in the neighborhood of the temporal fossa, the maxilla and the mandible. It becomes necessary,

TABLE 9.—*Relationships of Centers of Ossification of the Chondrocranium* *

Chondrocranial Regions	Centers of Ossification	Parts of Adult Skull
Occipital	Basi-occipital	Basilar process of occipital bone
	Exoccipitals	Occipital condyles
	Supra-occipital	Squamous portion of occipital bone below the superior nuchal line
Sphenoid	Basisphenoid	Body of sphenoid bone
	Presphenoid	Body of sphenoid bone
	Lingulae	
	Alae magnae	Greater part of alae magnae
	Alae parvae	Alae parvae
Periotic capsule	Petrous primordium	Petrous portion, Mastoid portion } of temporal bone
Ethmoid	Nasal septum (mesethmoid)	Lamina perpendicularis, Crista galli, Nasal septum (cartilage)
	Paranasals (ectethmoids)	Lateral masses of ethmoid bone, Superior conchae, Middle conchae
	Cribiform plates	Cribiform plates
	Inferior conchae	Inferior conchae
	Sphenoidal conchae	Sphenoidal conchae

* From Jordan and Kindred: A Textbook of Embryology, New York, D. Appleton & Company, 1926.

therefore, to delineate carefully the areas of bone derived from cartilage in the skull and to examine the twenty-two lesions recorded to determine whether their locations coincide with such cartilaginous areas.

Table 9 from Jordon and Kindred [32] summarizes the essential points in the histogenesis of the chondrocranium. The same information is duplicated diagrammatically in figure 42. Here the portions of the skull derived from cartilage are represented by areas in black, and in figure 43 the twenty-two lesions occurring in the skull have been plotted according to location. It will be seen at a glance that the giant cell tumors in the lower jaw which is the most frequent site for these tumors of the skull coincide in locality with centers of intracartilaginous ossifica-

32. Jordon, H. E., and Kindred, J. E.: A Textbook of Embryology, New York, D. Appleton & Company, 1926.

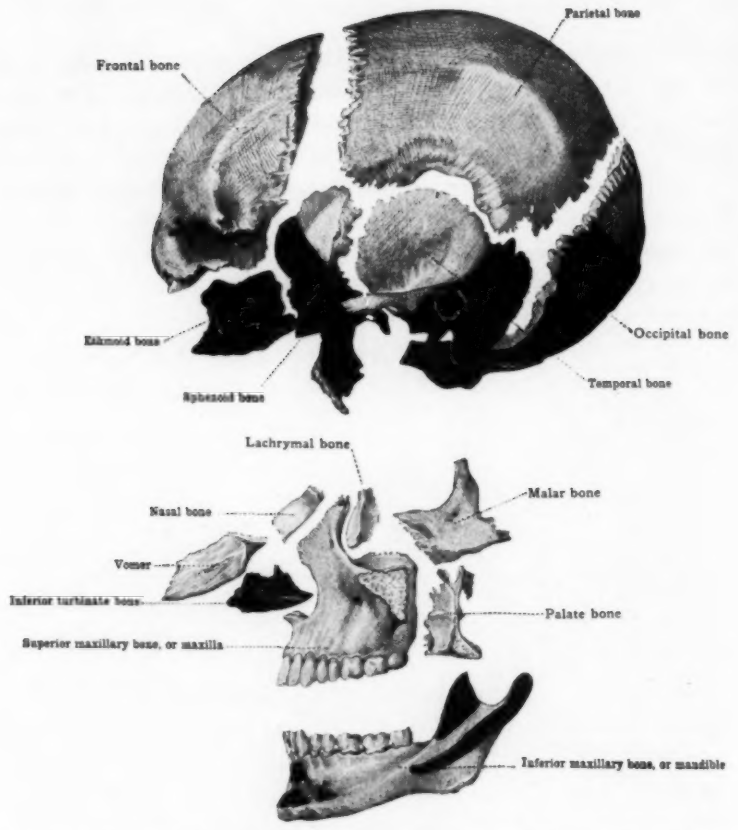

Fig. 42 (after Toldt).—The areas in black show the portions of the adult skull formed from cartilage; see table 9.

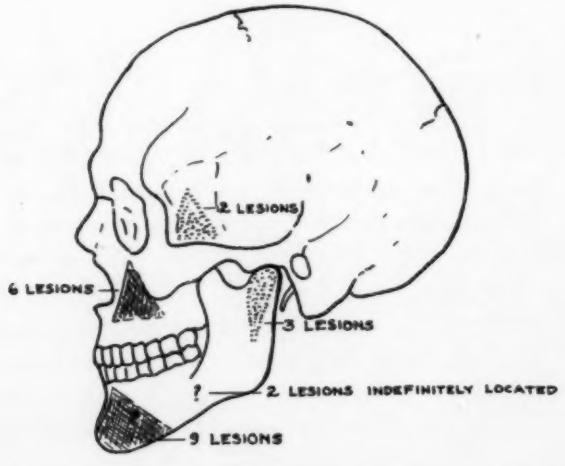

Fig. 43.—Diagram illustrating the location of twenty-two giant cell tumors of the skull. Compare with figure 42. See also tables 10 and 11.

tion for the mandible. The two lesions in the temporal fossa are associated with the wing of the sphenoid (which is derived from cartilage) projecting into this locality. These facts are further substantiated by

TABLE 10.—*Giant Cell Tumors of the Lower Jaw*

Path. No.	Date	Race, Sex, Age	Location	Symptoms	Operation	Microscopic	Results
42063	9/ 9/27	W. M. 13	Mandible at canine	Tumor 1 year	Curetting	Typical giant cell areas	Discharged well
36750	6/ 9/25	W. F. 12	Mandible, symphysis	Tumor 6 weeks	Curetting	Typical giant cell areas	Well 2 years
36182	1/ 7/25	W.	Mandible, ramus	Tumor	Resection	Typical giant cell areas	Discharged well
36170	12/ 9/24	W. F. 32	Mandible, symphysis	Tumor 1 year	Curetting	Spindle cell variant	Well 3 years
35246	4/10/24	W. M. 16	Mandible, symphysis	Loose teeth	Curetting	Spindle cell variant	Well 3 years
32991	5/15/23	W. F. 23	Mandible, ramus	Tumor 3 years	Curetting	Spindle cell variant	Recurred
29805	3/22/23	W. F. 42	Mandible, symphysis	Tumor 10 months	Curetting	Spindle cell variant	Discharged well
28392	6/21/21	W. M. 6	Mandible, ramus	Tumor 6 months	Curetting	Spindle cell variant	Discharged well
27281	10/21/20	W. F. 20	Mandible	Tumor 5 months	Curetting	Spindle cell variant	Well 1 year
27018	11/ 6/20	W. F. 41	Mandible, symphysis	Tumor 3 months	Curetting	Spindle cell variant	Well 6 years
15175½	1/ 0/14	W. M. 11	Mandible	Tumor	Curetting	Spindle cell variant	Well 9 years
7614	10/ 0/06	W. M. 10	Mandible, symphysis	Tumor 3 months	Resection	Spindle cell variant	Well 15 years
5227	1903	W. F. 13	Mandible, symphysis	Tumor	Resection	Spindle cell variant	Well 17 years
3034	4/14/00	W. F. 21	Mandible, symphysis	Tumor 10 months	Resection with glands	Spindle cell variant	Well 21 years

TABLE 11.—*Giant Cell Tumors of the Skull and Upper Jaw*

Path. No.	Date	Race, Sex, Age	Location	Symptoms	Operation	Microscopic	Results
37914	2/ 1/23	W. F. 52	Body of sphenoid	Pain 3 years	Excision	Typical giant cell	Hemiplegia 4 years later
15630½	8/ 0/03	W. F. 14	Temporal fossa	Pain 18 months	Excision	None	Well 20 years
43109	2/21/28	W. M. 9	Antrum, right	Tumor 6 months	Curetting	Spindle cell variant	Discharged well
37250*	11/ 2/25	W. F. 21	Antrum, left	Tumor 7 months	Explored	Giant cell areas	Well 3 years
37108	9/22/25	W. F. 13	Antrum, right	Tumor 2 months	Curetting	Spindle cell variant	Discharged well
29238	7/20/07	W. F. 18	Antrum and orbit	Tumor	Partial curetting	Spindle cell variant	Well 13 years
28946*	8/ 0/21	W. F. 25	Antrum	Tumor 7 months	Curetting	Spindle cell variant	Draining sinus
28698	8/21/11	W. F. ?	Antrum, left	Tumor 3 weeks	Resection	Spindle cell variant	Well 5 years

* Multiple tumors in other bones.

the data in table 10. In this table it is seen that in the mandible most of the giant cell tumors occur at the symphysis where Meckel's cartilage participates in the formation of this bone. The others are located at the ramus where there is a separate center for cartilaginous ossification. Table 11 also correlates the origin of the lesions in the temporal fossa

with cartilaginous centers in the sphenoid bone projecting into this region. The only discrepancy is apparently in regard to the six lesions of the upper jaw. In table 11, however, it is seen that all of these tumors found their way either into the antrum or into the orbital fossa. The ethmoid bone which is entirely derived from cartilage is in relation to both of these cavities as is shown in figure 44 *A* and *B*.

The fact that neither bone cysts nor giant cell tumors can be found in the portions of the skull which are entirely of membranous origin and the fact that they always occur at least in proximity to areas of cartilaginous ossification is more than suggestive if not convincing. Such evidence is worthy of scrutiny in more detail.

Giant Cell Tumors of the Temporal Fossa.—The history of two such cases are on file in the surgical pathologic laboratory. Only the

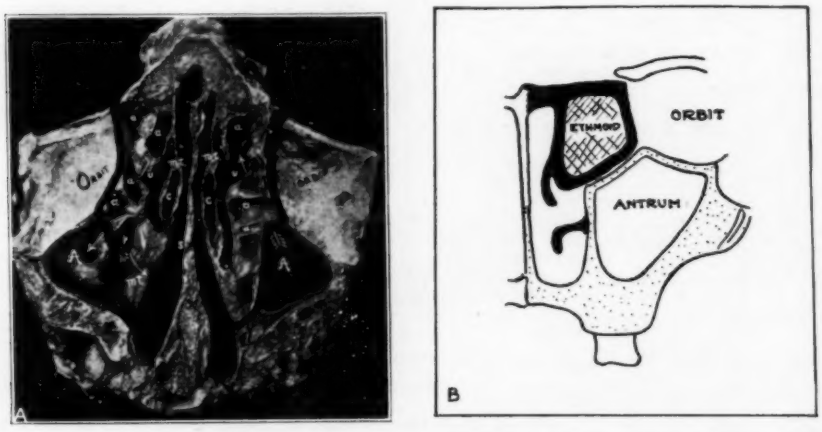

Fig. 44 (from Lothrop: Ann. Surg. **38**:233, 1903).—*A*, horizontal section above the level of the ostium maxillare. Within the figure, *A* indicates the antrum with arrows indicating the position of the ostium maxillare and lying in the infundibulum; *U*, uncinate process; the cavity just external to the letter is the infundibulum; *a*, *a*, anterior ethmoid cells; *p*, posterior ethmoid cells; *s*, septum nasi; *O*, orbital fossa; *m.t.*, middle turbinates. The posterior half of each turbinate is horizontal; the anterior half is vertical, and each instance the turbinate contains a cell (*c*). The dark space external to these turbinates is the middle meatus, and the long, dark area internal to the turbinates divided by the septum is the general cavity of the nasal fossa. The anatomic specimen shows the ethmoid bone which is formed from cartilage outlined in black and demonstrates the relation of this bone to the antrum and orbit. *B* (after Frazer: The Anatomy of the Human Skeleton, p. 245) is a diagram illustrating the position of the labyrinth of the ethmoid in relation to the orbit and antrum.

first is reviewed here because the records of it are complete in every detail. The patient was a white woman, aged 52, with pain near the right ear of three years' duration, and dizziness for six months. Exami-

nation showed deafness in the right ear, ataxia with deviation to the right, swelling over the right temporal region and a negative cerebrospinal fluid. At the operation the tumor was partially removed by excision. There was extension about the base of the pons which was deemed inoperable. Four years after operation the patient had a fully developed hemiplegia due to the continued growth of the tumor left behind. Under the microscope sections of the tumor showed a typical giant cell lesion

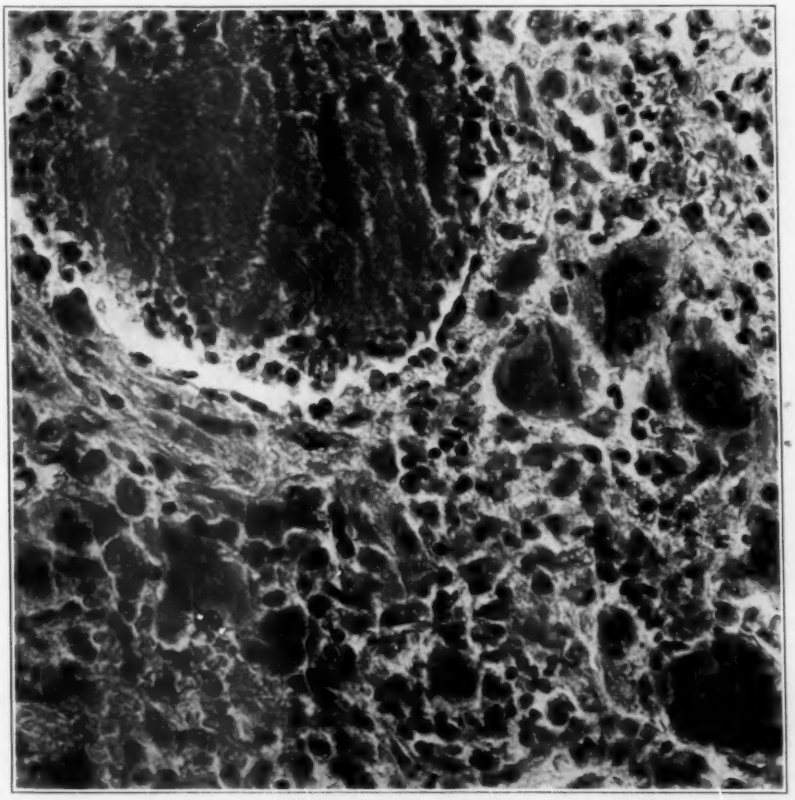

Fig. 45 (no. 37914).—A giant cell tumor arising from the body of the sphenoid and presenting in the temporal fossa. Attention is directed to the relation of the giant cells to the newly formed blood cavity.

(fig. 45). Careful inquiry into the operative notes shows that the origin of the lesion was from the posterior body of the sphenoid extending into the great wing around the carotid groove. This definitely relates the tumor to a center of cartilaginous ossification.

Giant Cell Tumors of the Upper Jaw.—All six of these tumors of the upper jaw presented into the antrum and one involved the floor of the orbit as well. Two of the six were multiple lesions occurring also

in other bones as will be seen from table 11. Tissue taken from the antrum was examined microscopically in every case except in the two multiple lesions, where tissue was taken from other bones (in one case the lower jaw, in the other the tibia), the histologic nature of the antrum tumors being inferred. In every case, the tissue was graded as a spindle cell variant of giant cell tumor, microscopically. In all of them careful search, where the records were sufficiently detailed, related these lesions to the ethmoid bone which would account for their origin from a cartilaginous center and the tendency of these tumors to present in the antrum or the floor of the orbit (fig. 44 *A* and *B*). Interestingly enough the illustration from Nélaton's work on giant cell tumors published in 1860 shows a lesion of the upper jaw, and the picture demonstrates clearly the relation of the tumor to the ethmoid bone and the inferior nasal choncha. We have reproduced this illustration in this article (fig. 46).

Giant Cell Tumors of the Lower Jaw.—Lesions in the mandible show a preference for the area between the symphysis and mental foramen. Occasionally one is located at the ramus. This unique distribution of these tumors is readily comprehended when the process is related to intracartilaginous ossification.

Unfortunately little regard has been paid in either the literature or the clinics to the exact location of giant cell tumors in the head. All the available cases studied by us support the belief that the origin of the pathologic process involved is at the sites of bone formed from cartilage and related to the normal resorptive process of bone by osteoclasts which takes place in the histogenesis of these bones. The predominant location of the giant cell tumor in the epiphysis of the long bones, it was seen, was in favor of this view. The fact that the membrane bones of the skull are not involved by either bone cysts or simple giant cell tumors confirms it.

EPULIS

The giant cell epulis of the jaws affords a strenuous proving ground to the concept of giant cell tumor advanced in this paper. For apparently in this group of benign lesions which occur on the gums and about the teeth there is no temporary bone undergoing resorption to stimulate the osteoclastic proliferation. Yet the characteristic giant cell in giant cell tumor is often described by the name of epulis, and under the microscope the basis of such terminology is plainly evidenced by the numerous large giant cells found in these growths.

Varieties.—Under the low power, the presence of stratified epithelium growing downward into the tumor from the mucous membranes of the gum must be relied on to differentiate many of these growths from

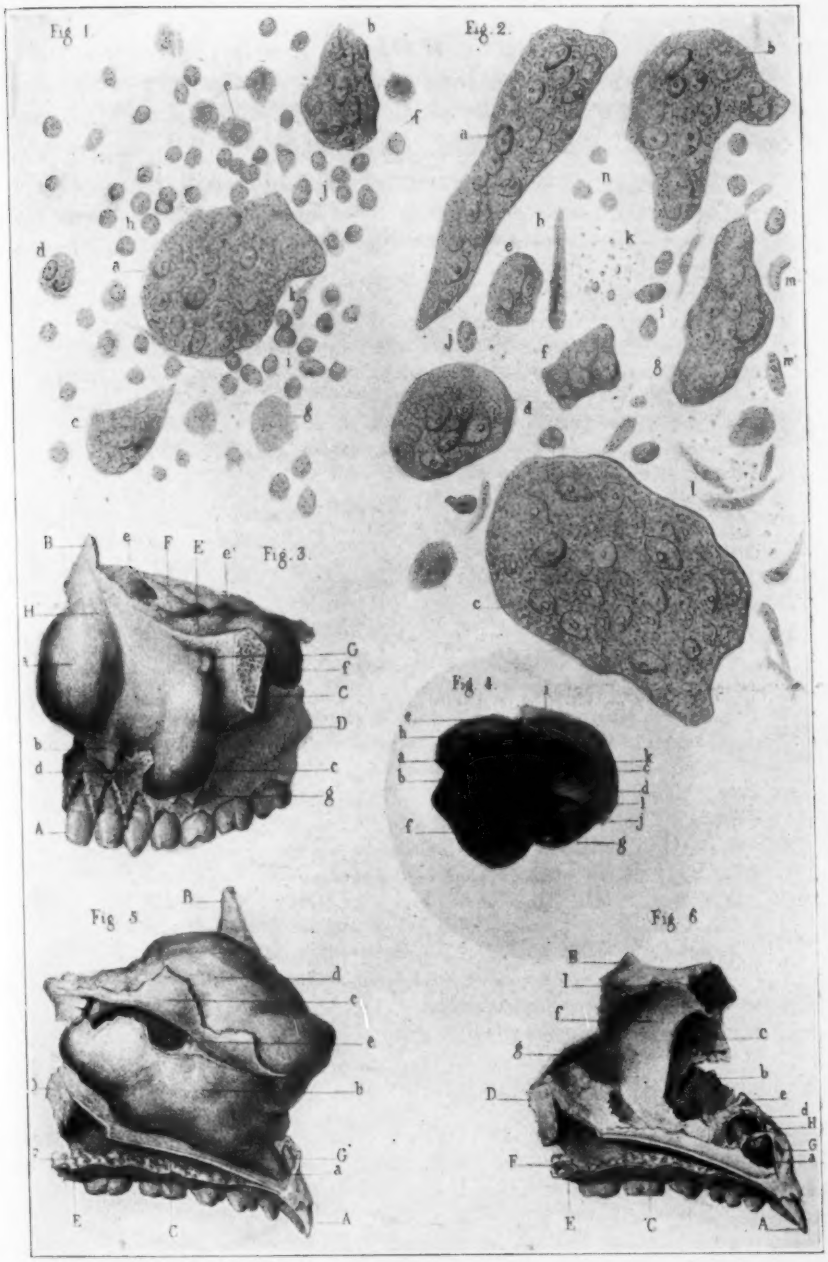

Fig. 46 (from Nélaton: Tumeurs benignes des os, 1860).—Illustrations of a tumor arising in the ethmoid bone and presenting through the antrum into the maxilla. The resection of the jaw shows nicely the location of the tumor in the turbinates, which are derived from cartilage. (The capital letters of the alphabet were used by Nélaton to refer to normal structures, the smaller letters to the neoplastic features. Their keys have been omitted because of their irrelevancy here.)

the typical giant cell tumor (fig. 47 *A* and *B*). The giant cells are of the usual multinucleated type and differ from those in the giant cell tumor of the long bones in no important detail. In the stroma of the epulis there is a tendency for a fibrous modification or a leukocytic infiltration to take place, and in special areas new bone formation of the fibro-ostosis type, such as is seen at the margins of the giant cell tumor and in the bone cyst, are frequently seen. These islands of bone are typical osteoid spicules with osteoblasts applied to their surface.

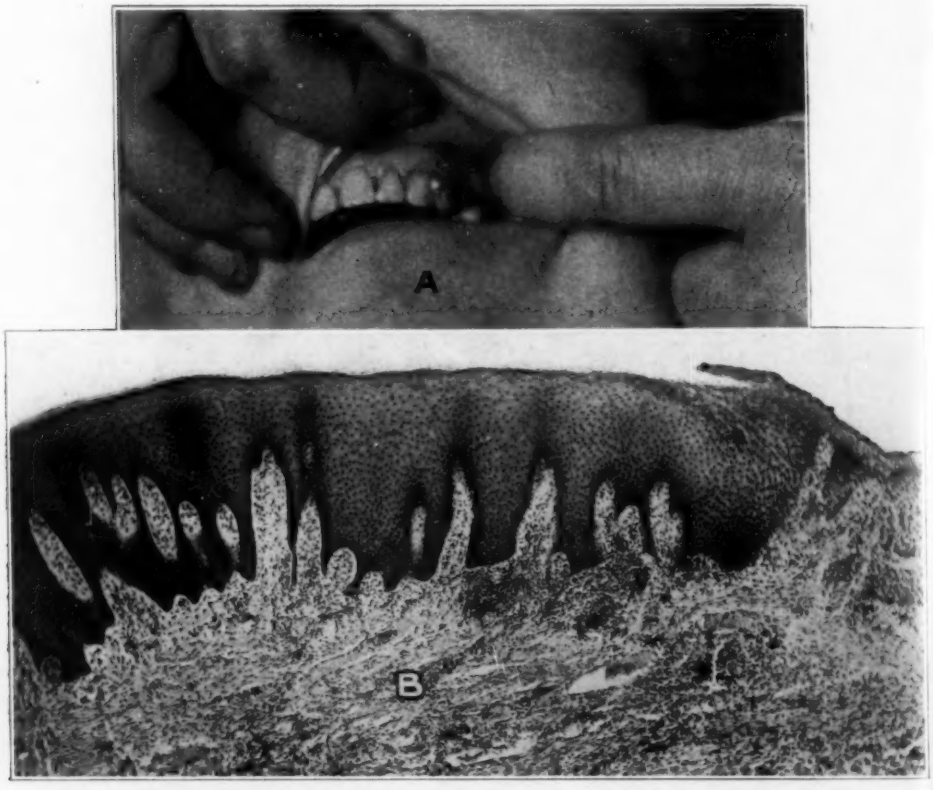

Fig. 47 (nos. 26824 and 36458).—Epulis of the giant cell type on the upper alveolar border. *A* illustrates the gross, and *B*, the microscopic. The giant cell areas are some distance from the mucous membrane and do not show well in this picture.

The foregoing description, however, is varied markedly in the so-called fibroid epulis. Here under the microscope, the tumor is practically always without giant cells. When these occur, they are sparse and small (fig. 48). The stroma is spindle and fibroblastic and in some places it is loose and edematous forming small evacuated cysts. In other places the fibroblasts are being transformed into osteoblasts which are laying down the intercellular substance of osteoid tissue. At points this

osteoid tissue is converted into true bony spicules of the same type seen in osteitis fibrosa. Organized hemorrhage is also present.

Microscopic analysis, therefore, divides epulis into a giant cell variety which is practically indistinguishable in its fundamental histology from giant cell tumor and a fibroid variety, which is the exact homologue of osteitis fibrosa. There are only minute variations such as a slight modification in the morphology of the giant cell in the first class of epulis and the tendency of the second class of epulis to be a solid structure

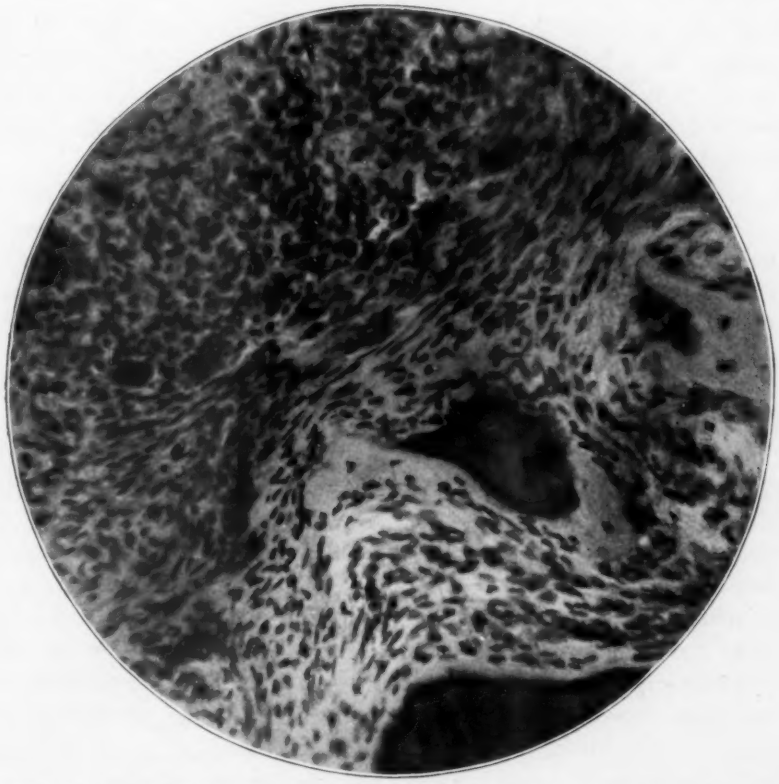

Fig. 48 (no. 23768).—Photomicrograph illustrating the fibroid type of epulis. Note the resemblance to osteitis fibrosa.

rather than a thin walled cyst. The conclusion that we are dealing with the same type of pathologic process here as in the cyst and the giant cell tumor in the long bones is unavoidable. Clinically and in the gross, however, the epulis is found only along the alveolar borders of the upper and lower maxillae which are membranous bones, and it is a periosteal rather than a medullary lesion.

These two facts constitute an apparent exception to the rule that giant cell tumor and its healing phase, osteitis fibrosa, always occur in the medulla of intracartilaginous bone as a consequence of a dysfunc-

tion in the normal osteoclastic resorption of this type of bone. The belief that the giant cell tumor is an exaggeration of such osteoclastic activity in the resorption of temporary bone, advanced throughout this paper, contests such an exception to the general rule, and demands that epulis be brought into intimate relationship with a normal osteoclastic hyperplasia.

Origin.—At the outset it is necessary to exclude from a diagnostic standpoint a large number of the cases usually classed as epulis. Many extraneous lesions such as hemangioma, fibroma, fibrohemangioma and fungating ulcers of infectious origin are erroneously placed in this category on the insufficient grounds that they occur on the gums. When this group is restricted on microscopic grounds to the lesions already described under the giant cell and fibroid epulis, a clinical entity is obtained which is more readily analyzed.

Epulides of this restricted category have been shown beyond peradventure to be periosteal in origin. Bloodgood [33] has shown that the lesions arise from the alveolar dental periosteum. They may arise either under the mucous membrane of the gum immediately surrounding a tooth or from the interior of the root socket itself. Besides this close association with the periosteum of the teeth, they occur only at the alveolar borders of the maxilla in the regions extending from the first molar on the one side to the first molar on the opposite side. An epulis practically never occurs behind or fastened to the root of the last molar and rarely at the site of any of the permanent molars. This point was emphasized by Scudder [34] in a review of 178 cases compiled from various clinics. They are most frequent near the canine and bicuspid teeth. Clinically, this relation to the teeth is further emphasized by the symptoms of the patient who gives a history of a carious tooth or some other dental irritation. The patient generally refers to the growth in its early stages as a gum boil, but the advanced stages may show a tremendous overgrowth of tissue protruding over the jaw and outside of the oral cavity. The growth of the epulis is outward and practically never invades the bone but pushes upward through the gums in the crevices about the teeth or in a fossa where a tooth has been pulled. The overgrowth and increase in size is never rapid until the tumor has escaped the confines of the alveolar border and is proliferating over the margins of the gum. The patients are most often children or young adults.

It is a consideration of these clinical features of epulis that gives a clue to the pathologic changes in this disease. First, they arise only

33. Bloodgood, J. C., on Epulis, Bryant and Buck: American Practice of Surgery **6**:818, 1909.

34. Scudder, C. L.: Tumors of the Jaws, Philadelphia, W. B. Saunders Company, 1912.

about the periosteal borders of certain teeth. Second, they practically never occur at the site of the molar teeth. Third, they expand outwardly and proliferate only after escaping the alveolar border. Fourth, they occur most frequently in children (not infants) and young adults. Again the age incidence and the site of the lesion are invaluable in disclosing the nature of the pathologic process. The unique features of the age limits and the failure of the epulis to occur about the molars relates these lesions to the deciduous teeth. For unlike all the other teeth the molars make only one appearance and that is a permanent one. If epulis can be related to the normal process of shedding the deciduous teeth which begins at the age of 6 and extends to the thirteenth year, the histogenesis of this process should explain the nature of the epulis and correlate the pathologic changes in this lesion with those in other giant cell tumors. This expectation is fulfilled when a study is made of the embryology of the teeth and the histologic process by which they are shed. Here the hyperplasia of osteoclasts seen in giant cell tumor is duplicated by an analogous process, in which there is a proliferation of odontoclasts that are instrumental in loosening and dissolving the roots of the deciduous teeth.

In more detail the histology is as follows: The anchorage of the deciduous teeth is by means of a thin layer of dental cement or cementum which surrounds the roots and is invested by a periosteal coat (or pericementum) which forms at once the outward coat of the roots and the periosteum of the jaw uniting the one to the other. The pericementum stops at the neck of the tooth and forms an annular thickening in conjunction with the dense connective tissue of the gum that is known as the circular dental ligament. The cementum itself is membranous bone and differs in no essential respect from this type of bone found elsewhere in the body. At about the age of 5 years odontoclasts arising from the pericementum or periosteum of the root proliferate and absorb the cementum of the roots of the deciduous teeth and thus open the way for the eruption of the permanent teeth (fig. 49).

About the roots of the deciduous teeth, therefore, there is a periosteum which is normally endowed with the power of osteoclastic hyperplasia. This osteoclastic hyperplasia is a normal occurrence after the age of 5 and is nature's provision for shedding the deciduous teeth. The process is analogous to the osteoclastic hyperplasia that occurs in the ends of the long bones and in the cartilaginous bones of the skull and is the natural method for the absorption of cartilaginous bone. The deciduous teeth, therefore, are in part like cartilaginous bone in that both are temporary bony structures and the pathologic process of giant cell tumor arises in connection with either, in one case giving origin to epulis and in the other the typical giant cell tumor of the long bones.

The fact that there is a fibroid type of epulis just as there is osteitis fibrosa in relation to giant cell tumor confirms this view. The fibroid epulis is the evidence of the healing reaction of the periosteum about the lesion. This healing reaction, like that everywhere in the periosteum

Fig. 49 (after Arey: Am. J. Anat. **26**:315, 1919-1920).—Giant cell osteoclasts about the roots of the deciduous teeth of young pigs. *ocl.* indicates giant cell osteoclasts; *mtx.*, matrix of teeth roots and *obl.*, osteoblasts.

and subperiosteal layers of bone, is an efficient defense against osteoclastasia or giant cell tumor. We have seen that it is capable of arresting a giant cell tumor or bone cyst in the shaft of a bone. At the epiphysis, however, where periosteum and cortical bone are deficient,

the giant cell tumor is progressive and breaks through. In the same way, in regard to epulis, the fibroid reaction (or as we choose to call it fibro-ostosis) is an efficient barrier to the tumor. It practically never invades the body of the jaw unless there has been undue trauma or some other factor. The ability of the epulis to progress and to proliferate over the gum, however, is due to the fact that periosteum ceases at the surface of the tooth, and it is through this gap about the teeth that the epulis erupts.

There are few other places in the body, to our knowledge, in which the periosteum is endowed normally with such osteoclastic proliferation as it is here at the alveolar border, although it is true as is demonstrated in the absorption of callus after fracture that all periosteum has some osteoclastic power. The unique situation, therefore, of epulis is readily comprehended. These tumors are connected with the shedding of the deciduous teeth, and the age incidence of them is related to the eruption of the permanent teeth as is shown in table 12.

TABLE 12.—*Age Incidence of Epulis in Relation to Eruption of Permanent Teeth*

Age of Eruption of Permanent Teeth *		Age Incidence of Epulis †	
First molars	6th year	5 to 10 years	6 cases
Two central incisors	7th year	10 to 20 years	17 cases
Two lateral incisors	8th year	20 to 30 years	7 cases
First premolars	9th year	30 to 43 years	9 cases
Second premolars	10th year		39 cases
Canines	11th and 12th year		
Second molars	12th and 13th year		
Third molars	17th and 25th year		

* Gray's Anatomy, ed. 21, 1924, p. 1134.
† All patients were over 5½ years and under 43 years of age. No lesions occurred at the site of the third molar.

It will be seen that there is a latent period or lag between the appearance of epulis and the shedding of the teeth. In other words there is an elapse of time between cause and effect which is due to the slow and benign course of these lesions. But the important point is that the epulis does not occur before the age of 5, and this is due to the fact that the permanent teeth do not begin to erupt until the age of 6. Instead of being an exception to the rule that giant cell tumor follows on a normal proliferation of osteoclasts, the epulis, therefore, presents valuable evidence in confirmation of this view. These lesions are related to a normal proliferation of the odontoclasts, and the process is best termed odontoclastasia which avoids the confusing miscellaneous group of conditions that for years have been carelessly thrown together under the term of epulis.

XANTHOMA

The view that the giant cell tumor arises as an abnormal phase in the osteoclastic resorption of cartilaginous or temporary bone demonstrates its usefulness when applied to the pathologic changes in the giant cell tumors of the xanthoma group. For here this conception enables

us to disprove the current endothelial and granulation tissue theories of these growths and to split off for the first time a clinical and pathologic entity from this chaotic group of lesions.

Varieties.—Since Lebert,[35] in 1845, introduced the term xanthos to denote a group of yellow fibrous tumors, a large and miscellaneous collection of entities has accumulated under that heading. A group of skin lesions under the names of xanthoma palpebrarum, xanthoma diabeticorum and xanthoma multiplex may be set aside here because giant cells are absent and untypical of this series. While containing lipoid pigments, blood pigment is usually wanting in these lesions. The xanthomatous tumors connected with the joints and tendons, however, frequently contain typical giant cell areas, and are related to the group of skin lesions mentioned only by their characteristic yellow color which has been shown definitely to be due to blood pigment or lipoids and hence nonspecific. Cells related to these lipoids and containing cholesterol have been referred to in the literature as foam cells and occur just as indiscriminately in this series of tumors as does pigment, being less frequent, but equally nonspecific. These foam cells also accompany at times typical giant cell areas in this collection of growths, and the presence of these cells in otherwise typical giant cell tumors of the long bones has led to the connotation of xanthosarcoma of bone by some authors.

Writers on the subject of xanthomatous tumors are agreed that this group comprises neither a clinical nor a pathologic entity. But since the giant cell areas have been viewed as nonspecific granulation tissue and both pigment and foam cells have been proved to be nonspecific, a criterion has been lacking wherewith to begin the analysis of this group of lesions into separate entities.

Nevertheless, since the time of Chassaignac[36] in 1852 and Billroth[37] in 1868, clinical peculiarities in regard to giant cell tumors of the tendon sheaths have repeatedly caused them to be set apart in this xanthoma group. More recently Tourneux[38] in 1913, Beekman[39] in 1915, Broders[40] in 1917, Garrett[41] in 1924 and Mason and Woolston[42] in

35. Lebert: Physiologie et pathologie, Paris, D. Baillière, 1845, vol. 2, p. 120.
36. Chassaignac: Gaz. d. hôp., 1852, p. 185.
37. Billroth, cited by Beekman: Giant Cell Tumors of the Tendon Sheaths, Ann. Surg. **62**:739, 1915.
38. Tourneux, J. P.: Les sarcomes des gaines tendineuses, Rev. de chir. **47**: 817, 1913.
39. Beekman, F.: Giant Cell Tumors of the Tendon Sheaths, Ann. Surg. **62**: 738, 1915.
40. Broders, A. C.: Benign Xanthic Extraperiosteal Tumor of the Extremities Containing Foreign Body Giant Cells, Ann. Surg. **70**:574, 1919.
41. Garrett, C. A.: Tumors of the Xanthoma Type, Arch. Surg. **8**:882 (May) 1924.
42. Mason, M. L., and Woolston, W. H.: Isolated Giant Cell Xanthomatic Tumors of the Fingers, Arch. Surg. **15**:499 (Oct.) 1927.

1927 have emphasized the tendency for these tumors to occur on the hand about the fingers and on the foot and about the ankle. Although the exact limits of the group were pathologically ill defined, Mason and Woolston [42] were able to collect 144 cases including eight of their own, placed in this class with reasonable assurance on the grounds of their characteristic location and peculiar histology. The clinical summary by these authors shows that the sexes are about evenly affected, that adults with an average age between 35 and 40 predominate, and that the size of these firm yellow tumors ranges between that of a pea and that of an egg. The course of the disease is typically benign but protracted

TABLE 13.—*Giant Cell Tumors of Tendon Sheaths*

Path. No.	Race, Sex, Age	Location	Trauma	Duration	Microscopic
42995	W. M. 38	Little finger, flexor surface.....	....	6 years	Typical giant cell areas
41193	W. F. 59	Index finger	....	.....	Typical giant cell areas
41039	W. M.	Finger	....	.....	Typical giant cell areas
40659	W. F.	Ring finger, flexor surface.....	....	4 years	Typical giant cell areas
39508	W. F. 16	Thumb, ulnar side.....	....	.....	Typical giant cell areas
38023	W. F. 13	Ring finger, flexor surface.....	Yes	13 months	Typical giant cell areas
35890	W. M. 38	Index finger, extensor surface..	Yes	5 years	Typical giant cell areas
35623	W. M. 17	Middle finger	....	.....	Typical giant cell areas
34381	W. M.	Index finger, flexor surface.....	....	2 years	Typical giant cell areas
32960	.....	Finger	....	.....	Typical giant cell areas
32480	W. M. 25	Index finger, flexor surface.....	Yes	1 year	Typical giant cell areas
31888	W. M. 7	Great toe, medial side.....	....	4 months	Bone and giant cell areas
29648	W. F. 30	Index finger, flexor surface.....	....	3 years	Typical giant cell areas
28997	W. F. 27	Middle finger, flexor surface....	....	10 weeks	Typical giant cell areas
28580	W. M. 50	Index finger, flexor surface, ring finger	....	1 year	Typical giant cell areas
27150	W. F. 18	Ankle	....	.....	Typical giant cell areas
26123	W. F. 33	Middle finger, multiple.....	Yes	3 years	Typical giant cell areas
21328	W. M. 24	Ring finger, flexor surface.....	Yes	5 years	Typical giant cell areas
20814	W. M. 45	Foot, metatarsal	....	30 years	Cartilage and giant cell areas
19030	W. M.	Hand	....	.....	Typical giant cell areas
15773	W. F. 58	Foot, instep, tarsal bones eroded	....	14 years	Typical giant cell areas
15237	W. M. 50	Ankle	Yes	3 years	Typical giant cell areas
14718	W. F.	Finger	....	.....	Typical giant cell areas
11004	W. F. 56	Index finger	....	.....	Typical giant cell areas
9137	W. M. 26	Foot	....	.....	Typical giant cell areas
3890	W. M. 30	Thumb, flexor surface.....	Yes	18 years	Typical giant cell areas
1620	W. M. 46	Ankle, medial side.....	....	22 years	Typical giant cell areas

(average duration four and one-fourth years), while trauma as an etiologic factor is present in from 30 to 60 per cent of the cases.

We have restudied this group of tumors and have had the privilege of checking the studies made by Garrett [41] in this laboratory in 1923 who reviewed 196 lesions of the joints, bursae, tendons and of the subcutaneous tissues. Our restudies with over 100 additional cases in the same groups accumulated since that time permit a segregation of twenty-seven lesions with a xanthic color composed of fairly typical giant cell areas, and the group thus histologically restricted presents more forcibly certain clinical and pathologic peculiarities.

As shown in table 13, eighteen of the twenty-seven lesions were located on the fingers at the metacarpophalangeal or interphalangeal

joints, and most of these were on the flexor surface. The remainder with few exceptions were elsewhere on the hand or about the foot and ankle. This predilection of the tumors for the tendons in special regions only is of more than passing significance.

Not only are the localities involved unique, but the histologic structure of these lesions is equally striking. Fibrosis of a marked degree akin to the spindle cell variant of giant cell tumor or to the fibroid type of epulis predominates the stroma about the giant cell areas. This

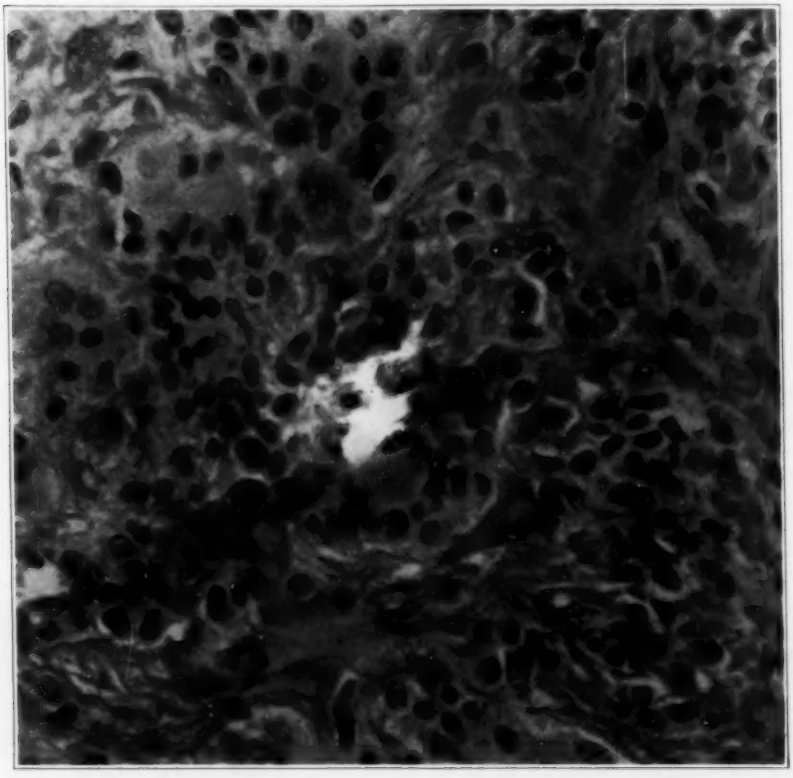

Fig. 50 (no. 42995).—Photomicrograph showing the high power of a giant cell xanthoma of the tendon sheaths. Note the network of intercellular substance, the giant cells and the numerous round cells. A few larger cells resembling cartilage cells are seen among the fibrous network.

fibrous tissue takes an unusually brilliant pink stain with hematoxylin and eosin and forms a peculiar lattice work in special areas enclosing cells that resemble cartilage cells (fig. 50). Giant cells of the usual epulis type, large and multinucleated, are numerous, and frequently average more than 30 to a low powered field. They are embedded in the usual round cell stroma typical of giant cell tumor, and conspicuously not the round cell infiltration seen in granulation tissue. Occasionally,

the foam cell characteristic of other types of xanthoma is present, but this type of cell has also been observed in 5 per cent of the giant cell tumors occurring in the long bones.

Under the microscope, pigment is a conspicuous feature of most of these tumors. As Smith [43] showed by his studies in this laboratory, this pigment is old blood pigment and gives the typical iron reaction.

Since we reject on histologic grounds the current granulation tissue theory of these lesions, it is necessary for us to demonstrate a connection between these tumors and some bony or cartilaginous structure. Heretofore attempts to establish such a relationship have failed, since tendons attach to the fibrous layer of the periosteum and bone only at their distal ends and the tumors under discussion are found not at this point, but in a more proximal position within the tendon sheaths.

Origin of Xanthoma of the Tendon Sheaths.—Fortunately there was available in the laboratory an important clue. A giant cell tumor of the patella was on record (table 7). Seven such tumors of the patella recorded as variants of either the bone cyst or the giant cell tumor have been reviewed by Cole,[44] and a personal communication from King and Towne [45] described a similar tumor of the patella the report of which has been published in the ARCHIVES OF SURGERY. The microscopic appearance of these tumors of the patella resembles the giant cell tumor of the tendon sheaths in regard to the large amount of pink-staining fibroid material. Still more important is the fact that the location of these tumors resembles the site of origin of similar tumors in the xanthoma group, in that the patella is embedded in a tendon, being a true sesamoid bone derived from cartilage.

The immediate inference suggested is that the giant cell tumors of the tendon sheaths arise in the sesamoid bones. The fact that these bones are derived from cartilage brings this inference into line with the conception of giant cell tumor pointed out in this paper and the fact that these sesamoid bones occur more frequently in the tendons of the fingers coincides with the location of these tumors described clinically.

A review of the embryology and anatomy of the sesamoid bone occurring in the human body supports the view that the giant cell tumor of the tendon sheaths arise from these bones. These bones must be regarded according to Thilenius [46] as integral parts of the skeleton

43. Smith, D. T.: Method for Making a Differential Diagnosis Between Xanthomatous and Melanin Tumors from Frozen Sections, Arch. Surg. **8**:908 (May) 1924.

44. Cole, W. H.: Primary Tumors of the Patella, J. Bone & Joint Surg. **7**: 637, 1925.

45. King, M. J., and Towne, G. S.: Primary Giant Cell Tumor of the Patella, **18**:892 (March) 1929.

46. Thilenius, cited by Bradley, O. C.: Anat. Anz. **28**:528, 1906.

phylogenetically inherited. Bradley [47] has shown that embryologically these bones are cartilaginous buds separating off from the joint side of the future bone just beneath the flexor tendon (fig. 51). The work of Pfitzner [48] has shown that the sesamoid bones are most frequent on the first, second and fifth digits of the hand and foot at the metacarpophalangeal or the metatarsophalangeal joints, but that they may occur at the site of these joints or the interphalangeal joints in all of the fingers and toes. Other, but more unusual, sites are in the tendons about the elbows, knee or ankle and in the tendon of the psoas muscle at the pubis

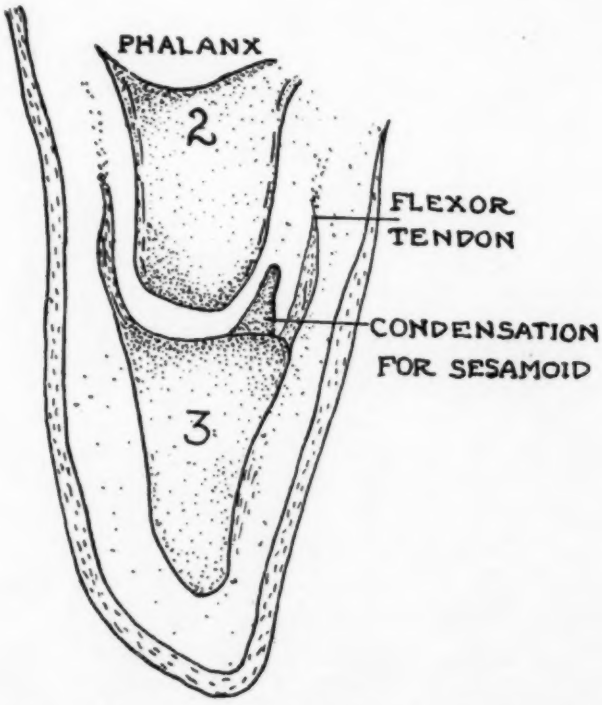

Fig. 51 (after Bradley: Anat. Anz. **28**:528, 1906).—Sketch showing the development of a sesamoid bone on the flexor side of a digit in a pig embryo 52 mm. long of forty days' gestation. The sesamoid bone, preformed in cartilage, is seen budding from the joint side of the distal phalanx.

or occasionally in the gluteus maximus near the head of the greater trochanter (table 14 and fig. 52).

In a study of the twenty-seven cases of giant cell tumors of the tendon sheaths in our own series and in a review of cases reported in

47. Bradley, O. C.: A Contribution to the Development of the Interphalangeal Sesamoid Bone, Anat. Anz. **28**:528, 1906.

48. Pfitzner, W.: Die Sesambeine des Menschen, Morphol. Arb. **1**:517, 1892.

the literature, all of those cases having typical giant cell areas were found to coincide in location with the sites of sesamoid bones. The occurrence of the sesamoid bones most frequently on the flexor surfaces of the fingers of the right hand is duplicated by these tumors. Mason and Woolston [42] in their review of 144 cases found the flexor surfaces of the fingers of the right hand most frequently affected, sixty-four of seventy-four tumors occurring on the flexor surfaces. On the lower extremities there is a similar coincidence in location, the xanthic giant cell tumors here occurring about the malleoli at the ankle and along the toes at the site of sesamoid bones. In the cases reported in the literature in which these xanthic tendon sheath tumors do not occupy the site of sesamoid bones, the microscopic reports show that they do not have the typical giant cell structures [49] and that they belong more properly to the fibrohemangiomas, fibromas or ganglion class, a point of

TABLE 14.—*Location of Sesamoid Bones in Man*

In the Upper Extremity	In the Lower Extremity
Flexor surface of the hand	Plantar aspect of the foot
Metacarpophalangeal joint—thumb	Metatarsophalangeal joint—great toe
Metacarpophalangeal joint—index finger	Metatarsophalangeal joint—second toe
Metacarpophalangeal joint—little finger	Metatarsophalangeal joint—little toe
Metacarpophalangeal joint—middle finger	Metatarsophalangeal joint—third toe
Metacarpophalangeal joint—ring finger	Metatarsophalangeal joint—fourth toe
Interphalangeal joint—thumb	Interphalangeal joint—great toe
Interphalangeal joint—Index finger	Interphalangeal joint—rarely second toe

Other Locations

Arm: Biceps brachii at radial tuberosity
Leg: Patella in quadriceps, peroneus longus at cuboid; tibialis anticus at first cuneiform; tibialis posticus at talus; head of gastrocnemius at lateral condyle of femur; psoas at pubis; gluteus maximus at greater trochanter; ankle tendons at both malleoli

view confirmed by our studies of more than 300 cases of this variety in the surgical pathologic laboratory.

The most convincing evidence that the sesamoid bones are the source of origin for these growths, however, is presented by the histology of the tumors themselves, for some vestige of the original structure of the sesamoid bones is usually visible under the microscope.

Special study on this point reveals the fact that the pink-staining network of tissue observed in the sections is the remains of white fibrocartilage from which tissue the sesamoid bones are known to be derived. The presence of this stroma containing cartilage cells confirms the origin of these tumors from the sesamoid bones. In several cases the calcification of this cartilage and transformation to bone were observed in the sections (fig. 53).

49. Since this paper was written the article by R. S. Rowland on "Xanthomatosis" has appeared (Arch. Int. Med. **42**:611 [Nov.] 1928). The erosion of the skull bones described by him is due to the tumors in the dura, and the few giant cells observed are phagocytizing dead bone, and are secondary to, rather than primary in, the xanthomatous tumors of the dura. Sections sent to the authors through the courtesy of Dr. Rowland do not show giant cell tumor.

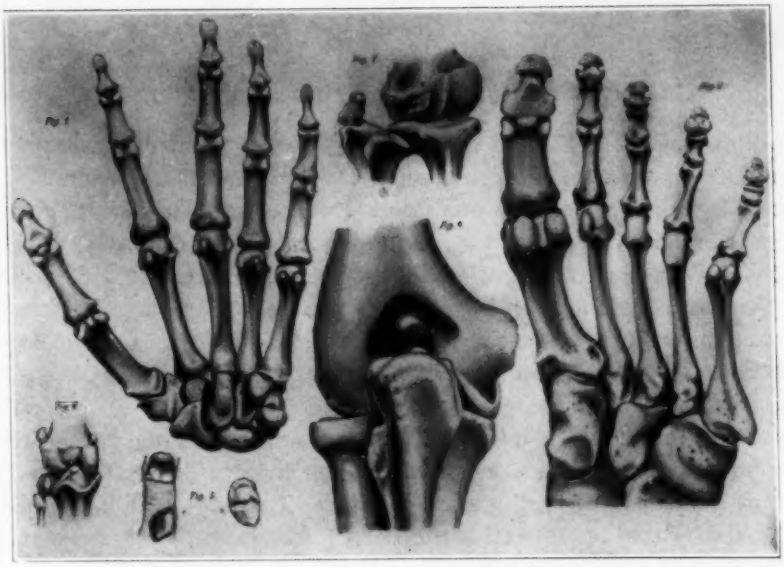

Fig. 52 (after Pfitzner: Morphol. Arb. **1**:517, 1892).—Anatomic preparations showing sesamoid bones in most of the localities in which they occur on the hand and foot and at the knee and elbow. Sesamoid bones occurring about the ankle are not shown in this illustration.

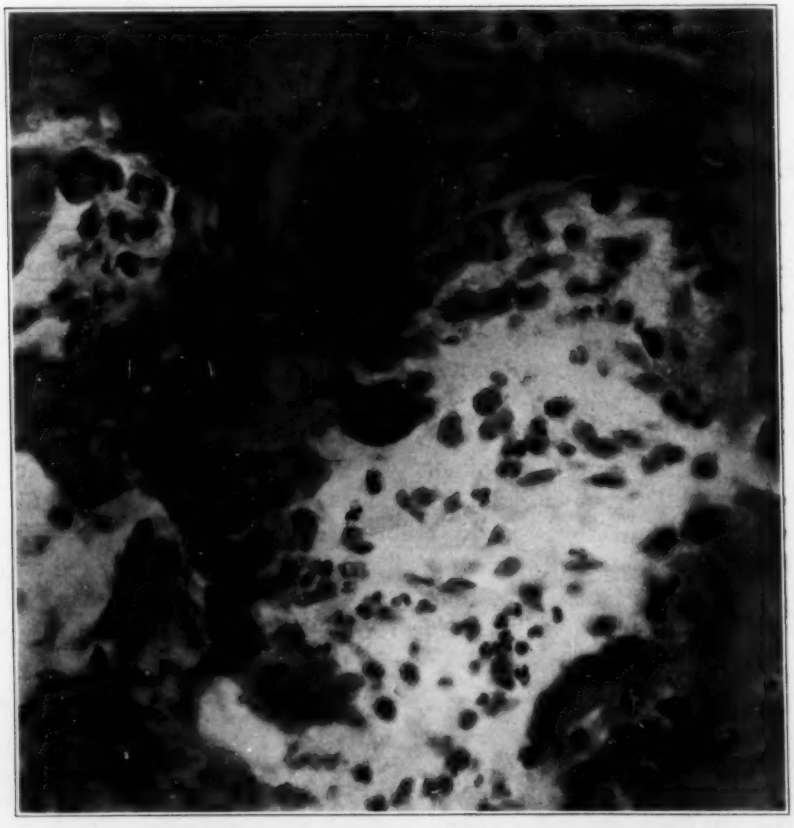

Fig. 53 (no. 31888).—Tumor of the sesamoid bone on the great toe. Bone derived from cartilage surrounded by giant cells is shown in the high powered photomicrograph. This tumor of the xanthoma group became infected and showed a healing reaction similar to osteitis fibrosa.

The peculiar yellow color of these tumors that has attracted so much attention differs from the deeper russet color of the giant cell tumor of the long bones because of changes in the blood pigment associated with age. These xanthic tumors have a much longer duration of symptoms (fifty months average duration as compared with fourteen months for giant cell tumors of the long bones), and their limited size is due to the small size of the bones affected and the resistance of the fibrous encapsulation, derived from the tendon sheaths. Adjacent bones are eroded on the side opposite the tendon sheaths, however, as is frequently recorded in the operative notes from many different clinics. In these small bones, compact bone, which promotes ultimate healing, is wanting, and a slow protracted course is the result.

From the foregoing it is seen that giant cell tumors of the tendon sheaths, which have long been erroneously classed under the heading of xanthoma are in reality tumors of the sesamoid bones, rather than of soft part structures. These sesamoid bones which are derived from fibrocartilage when affected by giant cell tumor emphasize again the relation of osteoclastic proliferation in bone newly formed from cartilage to the giant cell tumor.

The Xanthoma Variant of the Giant Cell Tumor of Bone.—Xanthoma or foam cells appear occasionally in giant cell tumors of the long bones. In the series of giant cell tumors (exclusive of those of the tendon sheaths) reviewed in this paper, these characteristic foam cells were found in only nine cases (fig. 54 *A*). These cells never predominated the picture and were relatively scarce, the tumor in the gross resembling the ordinary giant cell tumor. Although a case of xanthosarcoma of bone as described by Ewing [7] has never been observed in our series, we have noted foam cells in two cases of osteogenic sarcoma (fig. 54 *B*). Both of these cases have been reported in the literature, one by Goforth [50] and the other by Stone and Ewing,[51] with the diagnosis of malignancy in giant cell tumor. No note was made on the presence of the foam cells by these authors, but we observed them in a restudy of the sections.

A review of the nine cases of giant cell tumor with foam cells brings out nothing of significance other than the fact that the bone shell is perforated in these instances. The histology resembles that of the typical giant cell tumor without xanthoma cells, and clinically there are no unique features. The presence of two recurrent giant cell tumors and two so-called metastatic giant cell tumors in this series of xanthoma

50. Goforth, J. L.: Giant Cell Tumor of Bone, Arch. Surg. **13**:846 (Dec.) 1926.

51. Stone, W. S., and Ewing, J.: An Unusual Alteration in the Natural History of a Giant Cell Tumor of Bone, Arch. Surg. **7**:280 (Sept.) 1923.

variants is to be associated with the perforation of the bone shell by such lesions and not with an increased malignancy. The xanthoma cells are the results of the inclusion of lipoids from the soft parts about the tendons where the tumor is infiltrating, and obviously it is the extent of the destruction of the bony shell of the tumor and not the chance presence of foam cells that has clinical significance.[51a]

Giant Cell Tumors of the Soft Parts.—Because of their relation to the sesamoid bones a brief note is included here on so-called giant cell tumors of the soft parts. The records of only three such cases are available to us at this time. Two of these cases are from the surgical pathologic laboratory, and one is from the literature. In all of these cases we were able by location to relate the tumors to preceding bone.

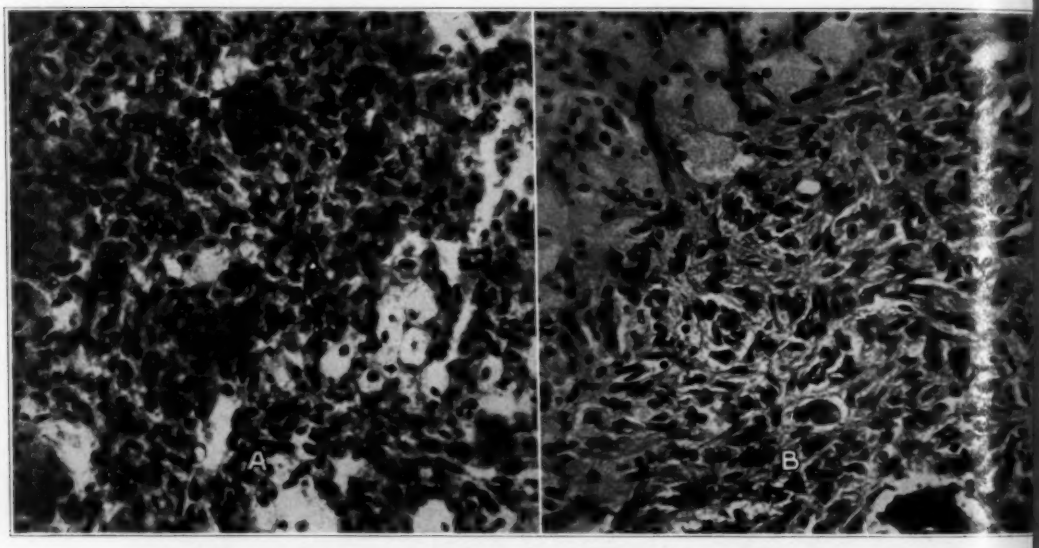

Fig. 54 (nos. 38238 and 40766).—Photomicrographs showing *A*, xanthoma cells in a typical giant cell tumor in the lower end of the radius, and *B*, xanthoma cells in an osteogenic sarcoma in the upper end of the tibia. The bony shell about the tumor was perforated in both cases.

The condition in the first case was diagnosed clinically as a recurrent mixed tumor of the parotid gland (fig. 55). The patient was a white woman, aged 23, with a tumor near the left ear of three years' duration. An incomplete removal of the growth had been performed eighteen months previously, and at the second operation a tumor the size of a

51a. The connection between the foam cells in these tumors and the lipoids derived from the tendons has been confirmed by a study recently called to our attention and published by Kusnetzowski (Virchows Arch. f. path. Anat. **263**:205, 1927).

hen's egg was found wedged in between the mastoid process and the angle of the jaw about the stylomandibular ligament. The pathologic diagnosis at that time was xanthoma of the parotid gland. A restudy of this case in this laboratory four years afterward showed it to be a giant cell tumor of the styloid process arising from the lower portion of the bone which has a separate center of cartilaginous ossification, and to which the stylomandibular ligament is attached. Thus the giant cell

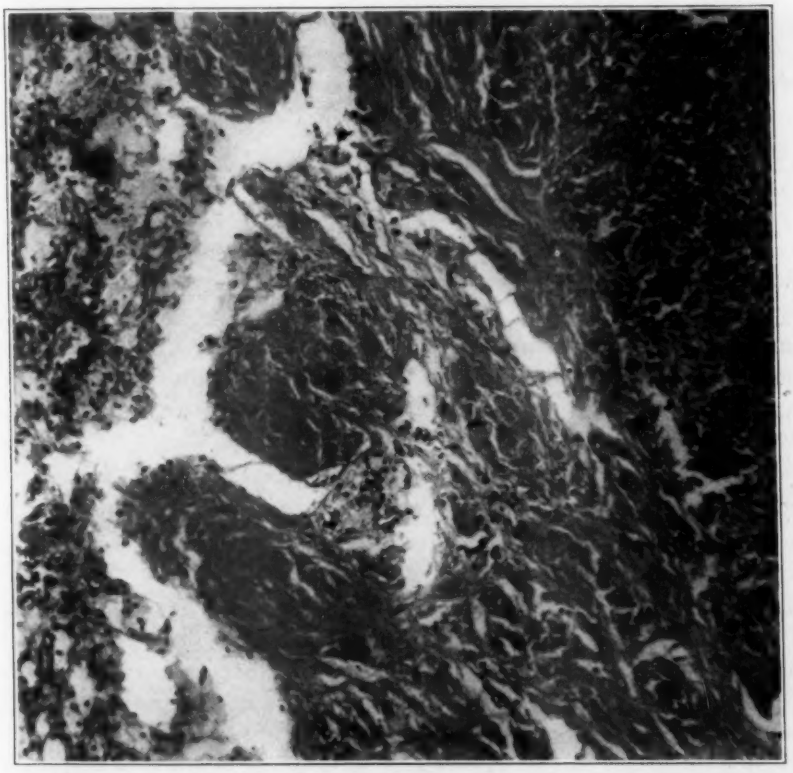

Fig. 55 (no. 35631).—Photomicrograph of a so-called xanthomatous tumor of the parotid gland. This tumor proved to be a giant cell tumor with foam cells arising from the styloid process of the temporal bone.

tumor tissue was related to cartilaginous bone and the foam cells in the tumor associated with a ligamentous structure.

The other two cases are related by location to sesamoid bones. One of these was described by Mallory,[28] who observed, "Foreign body giant cells are sometimes produced in such large numbers in reparative lesions not connected with bone that they may suggest a so-called giant cell sarcoma. An illustration of such an appearance is given for comparison. The giant cells followed some destructive lesion of the fat tissue over

the pubes (plate 28, figure 4)." This most extraordinary location coincides with the site of a sesamoid bone in the tendon of the psoas muscle where it glides over the pubic bone. Unfortunately, the unusual site of the lesion did not excite the curiosity of the author.

The last case is similar to this one of Mallory's in that it occurred in the head of the gastrocnemius muscle at the site of a sesamoid bone. Under the microscope the remains of the sesamoid bone were clearly visible, although the tumor had been diagnosed five years previously as a probable sarcoma of the soft parts.

While we have observed giant cells about bone displacing calcified necrotic tissue in tumors of the soft parts, as in the breast, we have never found typical giant cell tumor in such a locality, and we doubt that this tumor ever occurs under such conditions.

SUBPERIOSTEAL GIANT CELL TUMORS

Beside the giant cell tumors of the skull, of the aveolar borders and those of the sesamoid bones, another group of lesions assume a location significant for the interpretation of the pathologic nature of giant cell tumor. This group is the subperiosteal giant cell tumor which occurs in the shaft of the long bones and which presents certain unusual features that bear directly on the etiology of the lesions that we have been considering.

The subperiosteal giant cell tumor comprises a group of extremely modern recognition. Although periosteal giant cell tumors are described in older case reports, such cases on careful analysis prove to be typical giant cell tumors that have perforated their bony shell and grown extracortically with a fibrous reaction overlying them. The major portion of such tumors lies within the bone. What is here described as a subperiosteal giant cell tumor is a lesion beneath the periosteum that does not invade the bone to any significant extent. Only four such cases are in this collection, and lesions described of a similar nature are rarely reported in the literature. There is one excellent report by Cone [52] who described it as an ossifying hematoma. In this contribution the author who has long devoted himself exclusively to the study of pathologic changes in bone had the perspicacity to observe that "osteitis fibrosa, hemorrhagic osteomyelitis and giant cell tumor of bone have their representations in the microscopic pathology of this ossifying hematoma."

The data for the four cases comprising this series are summarized in table 15. In addition to the unique location of the lesions beneath the periosteum of the shaft the striking features brought out are: (1) the short duration of the symptoms (from two to eight weeks); (2) that trauma was the usual initial symptom and (3) that all cases have been recorded since January, 1926.

52. Cone, S.: Ossifying Hematoma, J. Bone & Joint Surg. **10**:474, 1928.

Evidently the diagnosis of subperiosteal giant cell tumor is dependent on an early roentgen examination of the patient following trauma. In the roentgenogram the periosteum is raised by a tumor casting little or no shadow which resembles a subperiosteal hematoma (fig. 56). At the operation an extremely thin capsule or shell of bone described by most operators as a blue dome presents itself, and when incised a cystic cavity containing blood is found. Tissue removed from this cavity and examined under the microscope shows a structure of typical giant cell areas intermingled with osteitis fibrosa. In every case there was uncertainty whether the condition should be termed a cyst or a giant cell tumor (fig. 57).

The explanation of these lesions is illuminating, their short duration, their clear relation to trauma and their appearance under the microscope yielding valuable information in regard to the sequence of the pathologic

TABLE 15.—*Subperiosteal Osteoclastasia* *

Path. No.	Race, Sex, Age	Site	Duration	Treatment	Microscopic
37442	W. M. 17	Femur cortical.....	6 weeks	Curetted	Giant cell areas, osteitis fibrosa
38372	W. F. 21	Ulna subperiosteal.....	8 weeks	Excision	Giant cell areas, osteitis fibrosa
39293	W. F. 58	Humerus subperiosteal.....	2 weeks	Curetted	Giant cell areas, osteitis fibrosa
40124	W. F. 16	Humerus cortical.....	8 weeks	Excision	Giant cell areas, osteitis fibrosa

* All lesions were observed since January, 1926.

events. In these cases it is clear that trauma and hemorrhage followed by separation of the periosteum (with a subperiosteal osteogenic layer of tissue) are the initial pathologic events. In the cortex beneath, a disturbance in the periosteal blood supply must occur, and in the periosteum above, some sort of healing reaction is sooner or later stimulated. The result is the mixture of giant cell areas and osteitis fibrosa which are seen under the microscope. That both factors are concerned in healing in this region is exemplified by callus formation and its resorption which forms commonly after most fractures. It is well known that an exuberant callus laid down by the periosteum will be eventually resorbed by osteoclastic activity. In the group of lesions under discussion the osteoclastasia that arises as a result of injury is rapidly regressive. The healing power of the underlying cortical bone and the overlying periosteum is evidently sufficient to heal over any abnormal activity of the osteoclasts. For this reason the duration of symptoms is short, and unless the patient comes under observation soon after injury and a roentgen examination is made, the lesions regress unrecognized, and disappear entirely or in unusual cases persist as a healed exostosis.

Our interest in these lesions is in the relation of hemorrhage following trauma to osteoclastasia. Evidently hemorrhage and a disturbance of the normal blood supply of bone act as a stimulus to the proliferation of osteoclasts and may in some cases lead to an abnormal osteoclastasia, or giant cell tumor. This conclusion means that in the study of the blood supply of the region of the epiphysis and in the factors that may disturb its normal functioning is to be found an explanation of the origin of the giant cell tumor. Some imbalance must arise in the rela-

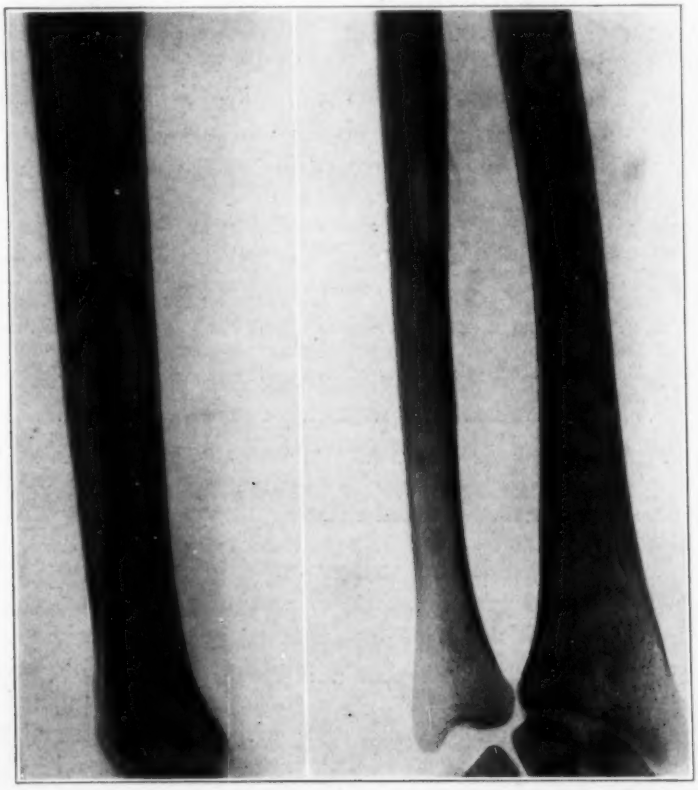

Fig. 56 (no. 38372).—Anterior and lateral x-ray views of subperiosteal osteoclastasia occurring in the shaft of the ulna. The lesion is eight weeks old.

tionship between the proliferation of osteoclasts and the reaction of fibro-ostosis, for apparently it is these two processes that participate in the healing of bone after injury and hemorrhage.

ETIOLOGY OF GIANT CELL TUMOR

It is much easier to discuss the etiology of tumor in terms of so-called etiologic factors than it is to point out the initial event and a subsequent unbroken chain of histologic consequences. For this reason,

the literature abounds with references to the etiologic factors of trauma and hemorrhage in the production of giant cell tumor and bone cysts. Konjetzny,[20] Lubarsch [53] and Pommer [54] are among those of the German school that have attempted to trace the bone cysts to medullary hemorrhage following trauma. We are in accord with these authors in placing

Fig. 57 (no. 39293).—Subperiosteal osteoclastasia of two weeks' duration. The photomicrograph shows the giant cells in relation to a newly formed blood cavity. Young fibrous tissue is attempting to repair the lesion. Microscopically, the tissue represents a borderline between giant cell tumor and osteoitis fibrosa.

53. Lubarsch: Die Bedeutung des Traumas zur Enstethung und Wachstum krankhafter Gewachse, Med. Klin. **41**:1651, 1912.

54. Pommer, G.: Zur Kenntnis der progressiven Hematom und Phlegmasieveränderungen (H. v. Haberers), Arch. f. Orthop. u. Unfall. chir., 1920, vol. 17.

trauma in a primary position in the production of these lesions. An attempt will be made, however, on the grounds of the embryologic observations pointed out earlier, to show just how trauma acts histologically in producing the bone cyst and the giant cell tumor.

Relation of Osteoclastasia to the Interruption of the Periosteal Blood Supply.—In the embryo, permanent compact bone is laid down by the perichondrium or subperiosteally, and, as we have seen, this cortical bone is a stronghold for the healing reaction of fibro-ostosis after injury. For nourishment, this bone is partially dependent on the periosteal blood supply. In young adults, this subperiosteal region is an extremely vascular and active tissue, and new bone formation proceeds here more rapidly than elsewhere. On the other hand, the most primitive cancellous bone in the medulla which undergoes reconstruction even in young adults by osteoclastic activity to form the medullary cavity is nourished by vessels in the medulla, the origin of which is from the nutrient artery. This cancellous bone of the epiphysis is supplied from vessels which anastomose around the joint, the diaphyseal, the metaphyseal and the epiphyseal, but as pointed out by Poland [24] and shown in injected specimens (fig. 58) by Lexer,[55] these vessels concerned with the major portion of the nutrition of both epiphysis and metaphysis pursue a periosteal and transcortical route.

The significance of this vascular arrangement in the origin of osteoclastasia has been implied in the discussion of subperiosteal giant cell tumor following trauma. The evidence in that group of lesions points to the fact that a vascular disturbance following trauma is a primary factor in the etiology of giant cell tumor.

A unique observation in regard to the site of early lesions of progressive osteoclastasia must now be recalled. Early giant cell tumors in the epiphysis (with a short history of trauma from two to six months previously) practically always assume an asymmetrical and subcortical location. In other words the giant cell tumor, and also the early bone cyst arise at a point just beneath the traumatized area of the cortex. This was pointed out in the study of the x-ray pictures and the gross specimens of these lesions and is again illustrated in the case shown in figure 59. Here the lesion is near the surface of the bone in one of the condyles of the femur. There was a definite history of trauma only two months previously as compared to the average duration of symptoms of fourteen months in giant cell tumor. The import of this subcortical location of the initial epiphyseal lesion has apparently been overlooked heretofore because the giant cell tumor during a later stage enlarges centrally at the expense of cancellous bone rather than out-

55. Lexer, E.: Die Enstehung entzündlicher Knochenherde, Arch. f. klin. Chir. **71**:1, 1903.

wardly against the more resistant cortical bone. The realization that the classic early giant cell tumor of from two to six months' duration practically always gives a history of trauma and shows a lesion subcortically at one side of the epiphysis furnishes an important clue to the etiology of this tumor. The site of the early lesion in relation to trauma suggests the cause of the imbalance in bone formation and bone destruction already referred to and demonstrates the sequence of events leading to progressive osteoclastasia.

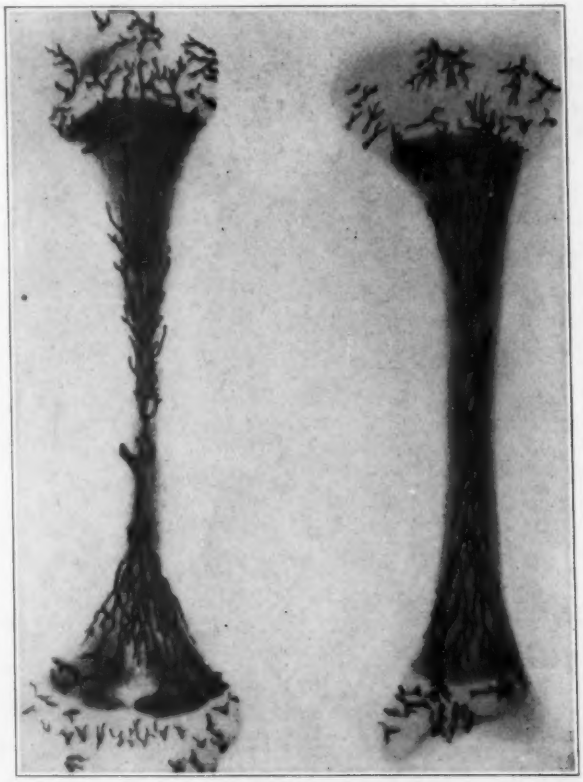

Fig. 58 (after Lexer: Arch. f. klin. Chir. **71**:1, 1903).—Injected specimens showing the epiphyseal blood supply in the long bones. The femur and tibia are represented.

Because of the prominence of the club-shaped epiphyseal region the cortical or outward edge receives the brunt of the trauma in this locality. This trauma acts mainly on the cortex in relation to its periosteum, avulsing the latter and interrupting the blood supply of the cortical bone. Normal vascular channels are thus supplanted by a subperiosteal hematoma. The effect of this interruption of the periosteal blood supply is to render inactive the cortical bone on this side of the epiphyseal end,

and the normal healing powers of this portion of the bone are suspended. The medullary circulation in the region of the epiphysis must take up an increased activity and by establishing new channels it works its way around the injured area to undertake the work of repair.

This increased function of the medullary blood supply during the interruption of the periosteal circulation can take place only after osteoclasts have opened up the channels in bone for the budding capillaries (for this we have seen is the normal order in histogenesis).

Fig. 59 (no. 20115).—Giant cell tumor of two months' duration in the epiphysis of the femur. Attention is directed to the subcortical location of the lesion and the staining of the surrounding tissue by old blood. The specimen illustrates the typical site of origin of the giant cell tumor.

But this increased osteoclastic activity in an area in which they are already unusually active in the rôle of new bone construction, occurs just at that time when unnourished cortical bone is undergoing necrosis. An imbalance is thus created between bone destruction by osteoclasts and new bone formation that would normally proceed from the reactive cortex were its circulation intact. The defensive reaction of cortical bone, therefore, is suspended while bone destruction by osteoclasts is at its heighth. This imbalance results in an unchecked hyperplasia of

the osteoclasts and produces a tissue characteristic of giant cell tumor and the early phase of osteitis fibrosa or bone cysts.

In the metaphysis, the reactive cortical bone which is thick and vascular, is apparently capable after a time of overtaking the osteoclasts. In the epiphysis, however, bone destruction seems to proceed at a faster rate than the thin cortical bone in this region can overtake. The result is an arrested lesion or bone cyst in the metaphysis, and a progressive or unchecked lesion in the epiphysis which is known as the giant cell tumor. Even in the epiphysis, however, the balance can be restored if surgical intervention occurs before the bone shell is too extensively destroyed. If the osteoclastic tissue is removed by the curet and cautery (and we suggest by aiding nature to collapse the bone cavity remaining), the giant cell tumor will also go on to ultimate healing.

Thus, histologically, trauma is related to the bone cysts and the giant cell tumor, not as an indefinite etiologic factor but as an initial event in disrupting the cortical blood supply which produces an imbalance between osteoclastic proliferation in the medulla and reactive compact bone in the cortex. In the etiology of these lesions individual variations in collateral circulation as well as the extent of the injury are important factors. That additional metabolic factors may enter into the production of this unbalance is shown by the analysis of multiple giant cell tumor and bone cysts presented in this paper, and the studies by Wilder [25a] on the serum calcium and phosphorus in these conditions. It is apparent, however, from the studies recorded here that the age of the patient, the site of the injury, the rate and extent of cartilaginous ossification at the end of the bone and the nature of the blood supply in the affected regions are the predominant factors in the pathologic process of bone cysts and giant cell tumors.

When all of these factors are considered, it is apparent why both bone cysts and giant cell tumors are rare in comparison to the frequency of trauma. It must be emphasized that to have the lesions clinically, an imbalance in two normal repair processes is necessary—an unusual increase of osteoclastic proliferation and a diminution or suspension of new bone formation in an injured cortex. These two processes are always active after injury. Both fibro-ostosis (osteitis fibrosa tissue) and osteoclastic proliferation (giant cell tumor tissue) are to be seen after ordinary fractures (fig. 60) and in the healing of a subperiosteal hematoma (Cone [52]). Only when the bone destructive phase of giant cell proliferation is in the ascendency for a significant period do the clinical entities of giant cell tumor or osteitis fibrosa arise.

The reasons for the distribution of giant cell tumors and bone cysts in certain favorite localities can now be pointed out. We know that the most frequent site of the solitary bone cyst is in the femur near the great trochanter and in the humerus near the greater tuberosity. These

are points of trauma at the hip and at the shoulder. Bone cysts, rather than giant cell tumors form at these sites because the epiphysis in the head of the femur and the head of the humerus are shielded from trauma and enclosed in the sheltered acetabulum and glenoid cavities. Trauma, therefore, reaches the shaft side of the epiphysis and a more resistant

Fig. 60 (general pathology, no. 58).—A healing fracture in a rib of a normal dog. Seven giant cells to the low power field are busy reforming the medullary cavity after callus formation. This illustrates the phase of osteoclastic proliferation in the normal healing process.

and better developed cortex of compact bone arrests these lesions after a time. On the other hand, in the lower end of the femur, the upper end of the tibia and the lower end of the radius, the epiphysis is exposed and

frequent trauma in these localities accounts for the prevalence of giant cell tumors at these points. In the upper end of the tibia, both the epiphysis and metaphysis at the tuberosity of the tibia are exposed to injury, and in this location both giant cell tumor and bone cysts occur. That these regions should be peculiarly susceptible to the trauma received is due to the active state of the bone-forming process in these localities. For, as Poland [24] has pointed out, "in the tibia and humerus the upper ends, in the femur and bones of the forearm, the lower ends, are in this respect (bone growth) the most active."

That it is locality alone that accounts for the difference between bone cysts and giant cell tumor can now be more clearly demonstrated. It has been pointed out earlier that the polycystic osteitis fibrosa is an earlier form of bone cyst. The short duration of symptoms, the vascularity and the giant cell areas confirm this. More important still the subcortical location of these lesions demonstrates that they have an identical mode of origin with the giant cell tumor. The infiltration of the giant cell areas by fibro-ostosis shows from the outset that they are destined to be arrested by a restoration of the balance between fibro-ostosis and osteoclastic proliferation.

It is also clear now just how pathologic fracture helps to heal a bone cyst. Not only does such an injury serve to collapse the rigid walls of the cavity, but in the area of shaft bone a fracture serves to reverse the process of circulatory disturbance already described.

The severing of the continuity of the shaft interrupts the medullary circulation and stimulates the periosteal blood supply, at the same time cutting off the nutrition of the osteoclastic tissue which receives blood from the medullary vessels. This process of circulatory changes following fracture has been ably reviewed by Robinson.[56]

Embryonic Histology in Relation to Pathologic Changes.—Since the time of Cohnheim [57] in 1877, the histogenic relationship of tumor has been inferred and speculated on, much data having accumulated in support of this view. But unfortunately Cohnheim placed emphasis only on the abortive products of embryology—cell rests—rather than on the histogenic processes in themselves. For this reason no painstaking effort to correlate the embryonic histology of the bone with the pathology of the bone tumors has ever been undertaken, to our knowledge. This most fruitful field of investigation has remained practically unexplored.

In advancing the knowledge concerning malignancy no possible realm of information can justifiably be neglected. The facts are many, con-

56. Robinson, W. H.: The Rôle of the Circulation in the Healing of Fractures, Arch. Surg. **17**:420 (Sept.) 1928.

57. Cohnheim, J.: Geschwülste, Allgemeine Pathologie, Berlin, 1877, vol. 1, p. 622.

nections few and hazy. Therefore, the correlation of the more fundamental facts of histogenesis, anatomy and physiology of bone, although difficult, is of first importance to the understanding of tumor formation in these structures. Perhaps at this stage of our knowledge it is even more to be desired than additional points in the clinical history. We have attempted here to bring the pathology into relationship with the more fundamental facts of histogenesis and physiology and to begin the larger undertaking of approaching tumors from this standpoint.

The primitive transformations in skeletal tissue—the stage of cartilaginous calcification, the stage of resorption of substitution bone and the final stage of permanent subperiosteal compact bone all have their corresponding pathologic significance. The function of direct bone formation from fibroblasts to osteoblasts to osteoid tissue, typical of the final stage of bone development, we have found to be instrumental as a healing reaction (fibro-ostosis) in the repair of bone and significant for the understanding of osteitis fibrosa. The function of bone resorption by osteoclasts followed by increased vascularity and the creation of medullary spaces, while a characteristic phase in the histogenesis of bone plays also a fundamental rôle in the production of giant cell tumor. And in the same way, the more primitive histogenic functions underlying the transformation and calcification of cartilage are reproduced in the pathologic process of osteogenic sarcoma. This last carries us into the realm of malignancy and sarcoma. It will form the theme of a subsequent paper.

SUMMARY

In an analysis of over 400 cases of tumors in the giant cell group a pathologic relationship was established between the bone cyst, giant cell tumor of the long bones and skull, giant cell epulis of the alveolar borders and giant cell tumors of the tendon sheaths. The usual bone cyst occurring in the metaphyseal region of the long bones of young patients was shown to be a healing phase of giant cell tumor—a conclusion based on clinical, pathologic and anatomic observations and demonstrated by an analysis of numerous transitional lesions between these two entities.

Giant cell tumors of the skull and long bones, epulides of the alveolar border, and giant cell xanthomas of the tendon sheaths were found to be fundamentally related to a transitional process characterizing the histogenesis of permanent bone, via the indirect route of substitution bone. This transition process underlying all of these tumors, as shown by embryologic studies, involves a proliferation of giant cell osteoclasts, the function of which is to initiate the canalization and vascularization of the preliminary calcified structure.

In the long bones the preliminary calcified structure, is calcified cartilage, and this is resorbed by a proliferation of giant cells in the epiphyseal region—a distortion of this proliferative process leading to giant cell tumor.

In the skull a similar giant cell hyperplasia characterizes certain cartilaginous centers of ossification, and giant cell tumors, it was demonstrated, occur only at such sites in the portions of the skull derived from cartilage and not in the membranous bones.

In epulides of the alveolar border, the temporary calcified structures are the roots of the deciduous teeth, about which giant cell odontoclasts proliferate, attacking the cementum to bring about shedding of these deciduous structures. Here again this normal giant cell proliferation forms the basis for giant cell tumors at these sites resulting in the epulis of the alveolar border.

In the so-called xanthomas of the tendon sheaths containing giant cells, the initial calcified structures are the sesamoid bones derived from fibrocartilage, and giant cell tumors of the tendon sheaths were shown to arise only at the sites in which these small bones are implanted in the tendons.

Evidence was advanced to show that the factor superimposed on this most important transitional giant cell proliferation, necessary to the production of giant cell tumor, was a disturbance of the vascular supply to these regions following trauma. But in each instance, the underlying normal histogenic function of giant cell proliferation was stressed as the essential factor, and it was pointed out that this histogenic basis necessitates the view that giant cell tumors are neoplastic and not inflammatory in origin. The importance of this histogenic conception for the analysis of other tumors was also emphasized.

THE RELATION OF THE ADRENAL GLAND TO THE TOXEMIA OF INTESTINAL OBSTRUCTION

AN EXPERIMENTAL STUDY *

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NEW ORLEANS

A rather considerable volume of experimental and controversial literature on the general subject of intestinal obstruction has appeared within recent years and has served to focus the interest of the surgeon on this interesting, and often most trying, condition. Much of interest has apparently been demonstrated as to both pathology and treatment, considerably more has been surmised and hypothecated, and still more is as yet unknown. From a practical point of view the alkalosis and dehydration which occur, particularly in so-called "high intestinal obstruction," and the diminished chloride content of the blood plasma, have served as valuable points of departure for therapeutic measures, but rather obviously the correction of such abnormalities partakes of the nature of symptomatic rather than curative treatment. The treatment for certain types of obstruction by the administration of spinal anesthesia has been successfully used by many clinicians, especially in the European clinics, and is rational in that such anesthesia may be made to ascend sufficiently high to block the inhibitor control pathway to the intestine by way of the white rami communicantes and thus prevent inhibitor impulses from spreading to the splanchnic nerves, a procedure which amounts to an actual reinforcement of the motor impulses which are normally continually reaching the intestine through the motor, or vagus, nerve supply; experimentally, the correctness of this line of reasoning has been partly, at least, substantiated by the observation that splanchnic anesthesia does actually tend to overcome obstruction by increasing the number and force of peristaltic contractions. However, even the restoration of normal motor power to the wall of the intestine apparently somewhat misses the mark, for a relatively tremendous number of experimental observations have accumulated which seem to demonstrate conclusively that the essential feature in obstruction is toxemia, particularly in those types of obstruction in which there is production of a closed loop or loops or in which strangulation occurs.

Since the latter types of ileus afford the most acute problem for the clinician, and since mild toxemia is almost undoubtedly a feature of the simplest of cases, the crux of the entire mechanism of intestinal obstruc-

* Submitted for publication, March 16, 1929.

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tion, from the clinical point of view at least, seems to be the source, mode of production, action, nature and neutralization of the offending toxin. Any extended study of the literature on this problem carries one through a veritable maze of observations unrelated or only partly correlated at present, some of which are actually contradictory and none of which in the present state of information gives immediate promise of a complete solution of the problem. Such theories as have been advanced are only partly explanatory and are largely at variance one with another.

In general, the only definite conclusions that appear to have been reached at present are that a toxin seems to develop in the lumen and possibly also in the wall of loops of intestine proximal to an obstruction, that this toxin probably is absorbed into the blood stream, and that it is most probably responsible for the toxemia.

The presence of such a toxin has apparently been demonstrated by a number of independent investigators. Murphy and Vincent,[1] Murphy and Brooks,[2] and Copher and Brooks [3] used the fluid contents of the lumen of the intestine above an obstruction virtually unchanged, simply putting it through a strainer or diluting it with water; the toxicity of such a fecal infusion, when injected, would scarcely seem to afford grounds for surprise, in view of its almost certain bacterial contamination. Dragstedt, Dragstedt and Chase [4] went a step further in that they strained and partially sterilized such fluid prior to injection by heating it to a temperature of 70 C. for an hour, and they further purified it by filtering away the coagulum thus formed; sterility was preserved with chloroform and toluene which in turn were removed, prior to actual injection, by means of heat and filtration. Clairmont and Ranzi [5] accomplished sterilization by a process of filtration through a Chamberland filter. Stone, Bernheim and Whipple [6] and Whipple, Cooke and Stearns [7]

1. Murphy, F. T., and Vincent, Beth: An Experimental Study on the Cause of Death in Intestinal Obstruction, Boston M. & S. J. **165**:684, 1911.

2. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Cause of Symptoms and Death, Arch. Int. Med. **15**:392 (March) 1915.

3. Copher, G. H., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Therapeutic Value of the Administration of Sodium Chloride, Ann. Surg. **78**:755, 1923.

4. Dragstedt, C. A.; Dragstedt, L. R., and Chase, C. S.: The Antigenic Property of Closed Intestinal Loop Fluid, Am. J. Physiol. **46**:366, 1918.

5. Clairmont, P., and Ranzi, E.: Zur Frage der autointoxication bei ileus, Arch. f. klin. Chir. **73**:698, 1904.

6. Stone, H. B.; Bernheim, B. M., and Whipple, G. K.: Intestinal Obstruction: A Study of the Toxic Factors, Bull. Johns Hopkins Hosp. **23**:159, 1912.

7. Whipple, G. H.; Cooke, J. V., and Stearns, T.: Proteose Intoxication and Injury of Body Protein: II. Metabolism of Dogs with Duodenal Obstruction and Isolated Loops, J. Exper. Med. **25**:479, 1917.

used the fluid contents either after heating to 60 C. for several hours, centrifugating and filtrating it, or after a process of autolysis in the presence of chloroform and toluene for a period of several days. Davis and Morgan [8] used both the mucosa of the intestine and its contents and prepared a toxin from these substances by admixture with sodium chloride in isotonic solution, addition of toluene and chloroform, autolysis at 37 C. for from two to ten days, heating to 60 C. for thirty minutes, centrifugation and final filtration.

In addition to the foregoing methods for the preparation of toxin, which are admittedly unsatisfactory in that a conglomeration of substances other than the actual toxic principle specifically sought must have been present in all of the products thereby obtained, two noteworthy attempts have been made to prepare the toxic agent in relatively pure form.

J. W. Ellis [9] described a method of preparing such a toxin by which he believed he had been able to obtain a relatively pure product; he considered this toxin directly responsible for the clinical observations in cases of ileus. He described the preparation of the toxin by the following steps: (1) the collection of the contents and mucosa of the intestine in 250 cc. of hot water; (2) thorough mixing and straining of this material through gauze; (3) the addition of five volumes of 90 per cent ethyl alcohol and subsequent filtration; (4) the boiling of the filtered precipitate with 100 cc. of distilled water; (5) the addition of 1 Gm. of magnesium sulphate after boiling away all traces of the alcohol left in the filtered precipitate, and the continuation of the boiling for a few minutes; (6) filtration, and the precipitation of the filtrate in five volumes of 90 per cent ethyl alcohol; (7) the filtration of this material and the drying of it in a desiccator, and (8) the dissolving, before use, of this material in from 25 to 50 cc. of water and subsequent dialyzation of this solution against distilled water for two hours.

Sugito [10] carried the process a step further, and was able to isolate a supposedly pure toxin not only from the mucosa and intestinal contents, but also from the blood serum of animals with intestinal obstruction. His process of preparation of such a toxin from serum (which is virtually the same as he used in preparing toxin from intestinal loops) consists of (1) heating the latter in boiling water until coagulation takes place; (2) cooling and incubating at 38 C. with an aqueous solution of trypsin and a small amount of toluene until complete digestion of the

8. Davis, D. M., and Morgan, H. S.: Natural Immunity of Animals Against Poison of Intestinal Obstruction, Bull. Johns Hopkins Hosp. **25**:39, 1914.

9. Ellis, J. W.: Cause of Death in High Intestinal Obstruction, Ann. Surg. **75**:429, 1922.

10. Sugito, S.: Ueber die Todenursache bei Ileus, Mitt. a. d. med. Fak. d. k. Univ. Kyushu., Fukuoka **9**:229, 1924.

coagulum has occurred; (3) filtration, coagulation in boiling water and refiltration; (4) addition of one and one-half volumes of saturated magnesium sulphate; (5) filtration through heavy filter paper; (6) solution of the collected precipitate in water and dialyzation in a collodion tube to remove the ammonium sulphate, (7) and reprecipitation with five volumes of alcohol.

There seems to be a general agreement among all the investigators who have worked on the preparation of toxin from the intestinal contents of animals with obstruction that a substance can be prepared relatively easily from such contents which is not present in the contents of normal intestine, which presents fairly definite physical and chemical properties and which, when injected, preferably intravenously, into normal animals, is capable of producing a clinical picture similar to the general clinical picture of intestinal obstruction itself, and ultimately death.

The toxic principle under discussion has been shown to possess the following properties concerning which most investigators are in agreement: 1. It is soluble in water. 2. It is not destroyed by boiling. 3. It is precipitated by five volumes of alcohol and by about 60 per cent ammonium sulphate. 4. It is not destroyed by pancreatic digestion for several days. 5. It does not pass through a collodion membrane when dialyzed against distilled water. Other properties have been described, but many of them either have not been sufficiently substantiated or seem in the present state of knowledge to be of no special significance. The properties mentioned are not, of course, sufficiently definite to establish with certainly either the exact substance or even the general class of substances to which the toxin belongs. Most investigators incline toward the opinion that it is a protein split-product; Stone, Bernheim and Whipple [11] and Whipple, Rodenbaugh and Kilgore [12] expressed the belief that it is a proteose; Wilkie [13] agreed with this idea; Stone [14] and Gerard [15] believed it to be a histamine or histamine-like substance; Ingvaldsen, Whipple, Bauman and Smith,[16] after careful analysis, came to the conclusion that it is a nucleoprotein. Other suggestions which have

11. Stone, H. B.; Bernheim, B. M., and Whipple, G. K.: The Experimental Study of Intestinal Obstruction, Ann. Surg. **59**:714, 1914.

12. Whipple, G. H.; Rodenbaugh, F. H., and Kilgore, A. R.: Proteose Intoxication, J. Exper. Med. **23**:123, 1916.

13. Wilkie, D. P. D.: Acute Intestinal Obstruction, Lancet **1**:1135, 1922.

14. Stone, H. B.: The Toxic Agents Developed in the Course of Acute Intestinal Obstruction and Their Action, Surg. Gynec. Obst. **32**:415, 1921.

15. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581 (Nov. 24) 1924.

16. Ingvaldsen, T.; Whipple, A. O.; Bauman, L., and Smith, B. C.: The Rôle of Anhydremia and the Nature of the Toxin in Intestinal Obstruction, J. Exper. Med. **39**:117, 1924.

been made are that it is trypsin, a toxic amine, a bacterial exotoxin, an endocrine secretion similar to the parathyroid hormone, cholin, an alkaloid or a ptomaine.

When injected, a toxin prepared according to any of the methods previously described produces a typical picture which includes vomiting, tenesmus, diarrhea, dilatation of the pupils of the eyes, tremor, weakness in the hind legs, weak, rapid pulse, decreased blood pressure and, in fatal cases, death in a state of coma—a picture, as previously mentioned, that corresponds reasonably closely with the clinical picture of experimentally produced ileus.

OUTLINE OF THE PROBLEM

During the course of some experiments on ileus previously reported, I had occasion numerous times in the last several months to employ especially the methods of Ellis and of Sugito in the preparation of toxin in both rabbits and dogs, and my results in general were strictly in accord with the published results of these investigators. However, I have never been able by chemical means to isolate from the blood serum of these animals a toxin by the methods outlined by Sugito, which, when injected into normal animals, would cause their death, although I have made many attempts. Failure to accomplish this was first attributed to the rather inexplicit directions given by Sugito for deriving the substance, but after having devoted considerable time and attention to the matter and after trying many different variations of chemical technic, the statement made by Sugito with reference to his own work with the method that, in spite of the fact that he had derived his toxin from relatively large animals, he had been able to produce death only in very small ones began to acquire considerable significance as offering a fairly obvious explanation for previous failure. Reflection on these facts gradually crystallized itself into two correlative propositions: (1) either so much of the toxin must have been lost during the process of chemical preparation that the amount finally recovered was insufficient to kill animals of anywhere near comparable size, or (2) as the result of the action of the toxin in the animal with intestinal obstruction extending over some considerable period of time, certain organic changes of an undetermined nature must have so debilitated the animal that an amount of toxin sufficient either to kill it or at least to bring it to the agonal state was insufficient to kill another animal of reasonable size.

At about the same time that attempts to prepare toxin from obstructed loops of intestine had been begun, routine histologic examinations of organs of a considerable number of animals dying from the effects of obstruction were studied, and this procedure seemed fairly definitely to demonstrate that characteristic degenerative changes usually occur in the adrenal glands of such animals. Of course, the general

protective function of the adrenal glands has been recognized for a number of years. Boinet,[17] in 1896 and 1897, was apparently the first to observe that animals which had undergone double adrenalectomy were more sensitive to toxic substances than normal animals, and this pioneer work has received confirmation at the hands of many more recent observers. Scott [18] showed that the resistance of adrenalectomized rats to morphine, killed bacteria, and histamine was greatly reduced; Marine [19] and Jaffe showed the same for standard typhoid vaccine; Belding and Wyman [20] for diphtheria toxin, and Crivellari [21] for potassium cyanide, nicotine, acetonitrile and histamine. Lewis [22] showed decreased resistance of adrenalectomized animals for cobra venom, curare, veratrine and morphine.

Accordingly, the problem of ascertaining the possible rôle of the adrenal glands in protecting the body economy against the toxin of intestinal obstruction was not far to seek.

OUTLINE OF THE EXPERIMENTS

The experiments that I am about to detail concern themselves with this problem. The general method was the obvious one adopted by the authors mentioned latterly in their investigation of the protective mechanism of the adrenal glands against the various other toxins enumerated. A series of animals was prepared by double adrenalectomy. A similar series of normal ones was used as controls. Half the toxin derived from the intestinal contents and mucosa of an animal with artificial obstruction was injected into an animal in the adrenalectomized series, and the other half into a corresponding animal in the normal series. The animals in both series were kept under observation until death or until the effect of the toxin had disappeared.

(*a*) *Selection of Animals.*—Only two of the ordinary laboratory animals are available for experiments involving survival after double adrenalectomy, the rat and the rabbit, since these are the only common laboratory animals that survive the operation of double adrenalectomy for any considerable length of time. Furthermore, since the preparation of toxin from obstructed loops of intestine involves

17. Boinet, E.: Diminution de résistance des rats doublement décapsules a l'action toxique de diverséssubstances, Compt. rend. Soc. de biol. **49**:466, 1897.

18. Scott, W. J. M.: Influence of Adrenal Glands on Resistance; Susceptibility of Adrenalectomized Rats to Morphine, J. Exper. Med. **38**:543, 1923; Influence of Adrenal Glands on Resistance; Toxic Effect of Killed Bacteria in Adrenalectomized Rats, ibid. **39**:457, 1924; Influence of Adrenal Glands on Resistance; Susceptibility to Histamine as Test of Adrenal Deficiency, ibid. **47**:185, 1928.

19. Marine, D., and Baumann, E. J.: Duration of Life After Suprarenalectomy; an Attempt to Prolong it by Injection of Solution Containing Sodium Salts, Glucose and Glycerol, Am. J. Physiol. **81**:86, 1927.

20. Belding, D. L., and Wyman, L. C.: Rôle of Suprarenal Gland in Natural Resistance of Rat to Diphtheric Toxin, Am. J. Physiol. **78**:50, 1926.

21. Crivellari, C. A.: Sensitiveness of Adrenalectomized Rats to Certain Toxic Substances, Am. J. Physiol. **81**:414, 1927.

22. Lewis, J. T.: Sensibilité des rats prives de surrénales envers les toxiques, Compt. rend. de l. Séances Soc. de Biol., Jan. 22, 1921.

the use of chemical methods, it is readily apparent that the larger the amount of material available at the beginning of the process of preparation, the more likely does the obtaining of a suitable amount of the final product become. Also, it seemed highly desirable to use the same animals for the production of the toxin as for the reception of it by injection. For these reasons, it seemed desirable

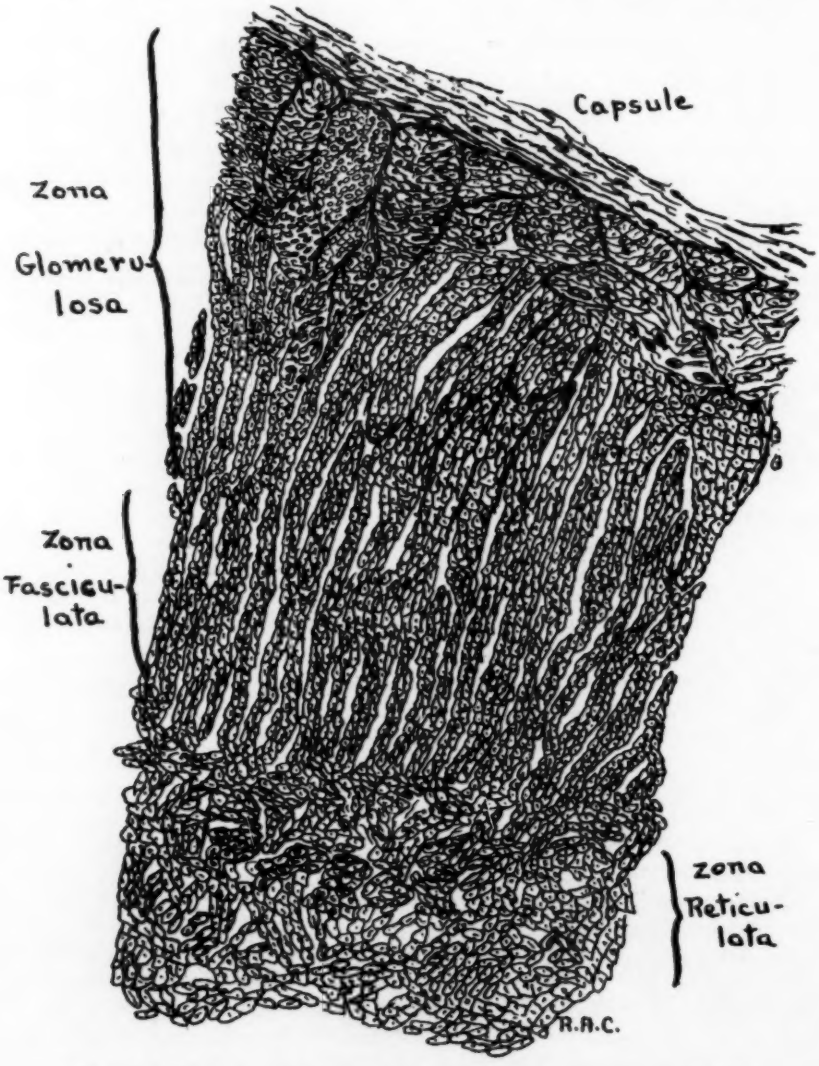

Fig. 1.—Normal suprarenal cortex in the dog; low power sketch.

to use the larger animal, that is, the rabbit. Rabbits weighing from 1 to 1.5 Kg. were obtained.

(*b*) *Technic of Obstruction and Preparation of Toxin.*—Intestinal obstruction was produced in these animals by tying a piece of ordinary cotton tape tightly about the terminal part of the small bowel, under ether anesthesia, under

strictly aseptic conditions, and with the usual surgical technic. Animals thus prepared were returned to their cages and were kept until they became virtually moribund. It was soon found that animals thus treated survived rarely for much longer periods than forty-eight hours, and this was the time limit maintained for killing them preliminary to the preparation of toxin from their obstructed intestinal lumina. The animals were killed, the entire small intestine above the point of

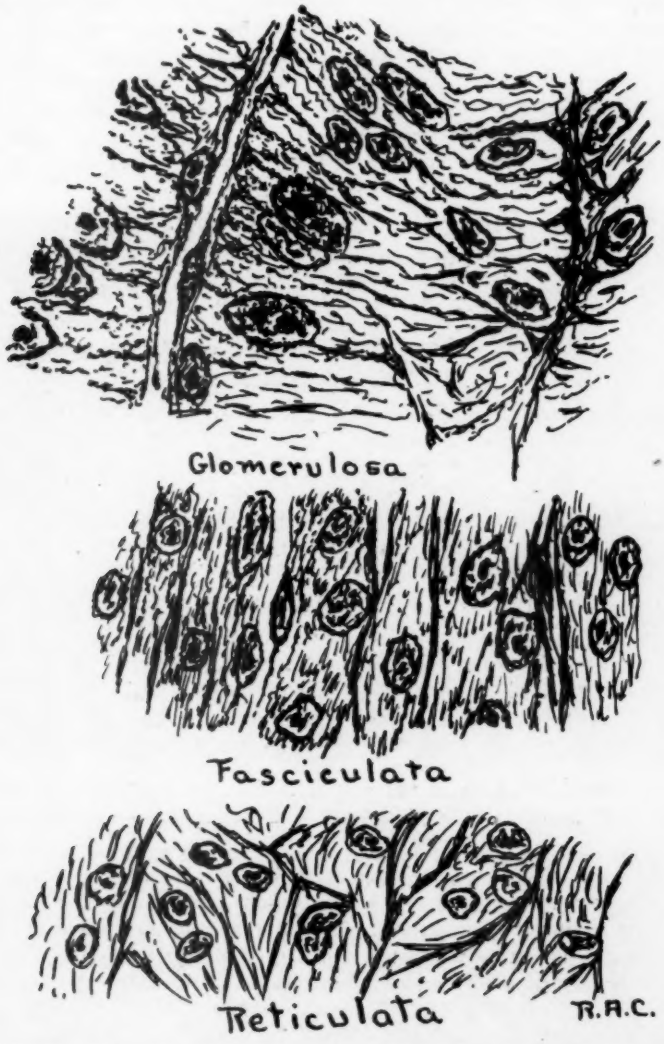

Fig. 2.—Normal suprarenal cortex in the dog; high power sketch.

obstruction up to the pylorus of the stomach being excised in one piece immediately after the production of death by an overdose of ether. The mucosa and contents were removed and this material was placed in a mortar; a small quantity of clean sand was added, and the entire mass was thoroughly rubbed up and macerated with a pestle. This mass was then extracted with water, precipitated with alcohol, and otherwise prepared according to the method of J. W. Ellis, except that, because

of the relatively small amount of material, 100 cc. of water instead of 250 cc. was used for the initial extraction, and correspondingly smaller amounts of the various other ingredients during the course of the preparation.

(*c*) *Preparation of the Doubly Adrenalectomized Series.*—Animals were prepared for the injection of this toxin by double adrenalectomy, the adrenals being removed by the posterior or kidney route, great care being taken to remove both glands intact in every case. Prior to the injection of the toxin, adrenalectomized rabbits were allowed to survive for a period of two or three weeks, in order that they might fully recover from the effects of the operation and that any abnormalities following the injection of the toxin might reasonably be interpreted as due to it and not to any factor directly associated with the technic of the operation. No attempts were made to select rabbits with any particular care, either for the production of obstruction or in the case of the double adrenalectomy preparation.

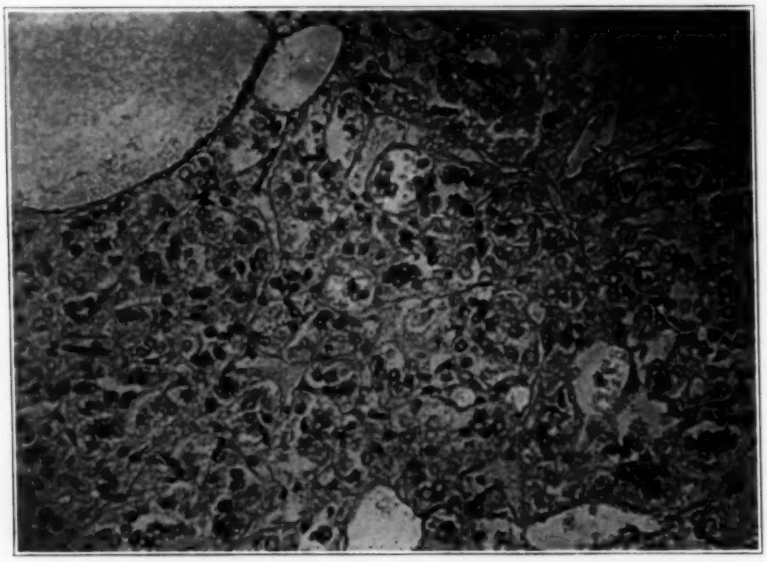

Fig. 3.—Adrenal medulla in the dog following the production of ileus; low power photomicrograph, showing blood vessel dilatation and pseudo clot formation.

The rabbits were fairly large, weighing from 1 to 1.5 Kg. apiece. Some of them were angora, some were ordinary albino rabbits, while others were gray or yellow, many of them being piebald. During the course of the experiment no particular effort was made to control the diet of the animals; this consisted in all cases of bread and lettuce and as much water as the rabbit desired, together with grain in the form of oats.

Twenty-six rabbits were adrenalectomized during the course of the experiment, and of these only six survived the performance of the operation for a suitable length of time.

DOUBLE ADRENALECTOMY

RABBIT 1.—An albino female rabbit weighing 1.6 Kg. was operated on on Aug. 22, 1928. The operation was started at 2 p. m., and completed at 2:35 p. m. There was considerable hemorrhage. The animal reacted from the anesthetic, but died at 3:30 p. m. of hemorrhage.

RABBIT 2.—A piebald female rabbit weighing 1.5 Kg. was operated on on Aug. 22, 1928. The operation was started at 3:05 p. m. and completed at 3:50 p. m. There was considerable hemorrhage. The animal did not react from the anesthetic, and died at 3:55 p. m.

RABBIT 3.—An albino male rabbit weighing 1.1 Kg. was operated on on Aug. 22, 1928. The operation was started at 4:22 p. m. and completed at 4:40 p. m., and the rabbit was returned to his cage in apparently good condition. At 6:30 p. m., however, it was found dead. Autopsy showed the cause of death to be hemorrhage.

RABBIT 4.—A piebald male rabbit weighing 1.4 Kg. was operated on on Aug. 22, 1928. The operation was started at 4:55 p. m., and the animal was returned to his cage at 5:34 p. m. It reacted from the anesthetic, but died at 6:20 p. m. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 5.—An albino female rabbit weighing 1.2 Kg. was operated on on Aug. 24, 1928. The operation was commenced at 2:13 p. m., completed at 2:52 p. m., and the animal was returned to its cage apparently in good condition. It reacted from the anesthetic, walked about the cage, and survived for the remainder of the afternoon, but was found dead the following morning. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 6.—An albino female rabbit weighing 1.2 Kg. was operated on on Aug. 24, 1928. The operation was commenced at 4:22 p. m. The adrenals were fragmented during the course of the operation, and there was considerable hemorrhage. The operation was completed, and the animal was returned to its cage about 4:52 p. m. It was found dead at 5:28 p. m. Autopsy revealed the probable cause of death as hemorrhage.

RABBIT 7.—An albino female rabbit weighing 1.4 Kg. was operated on on Aug. 24, 1928. The operation was begun at 5:01 p. m. The adrenals were fragmented during the process of removal and considerable hemorrhage was encountered. The animal was returned to its cage at 5:38 p. m. apparently in a moribund condition; it survived only a few minutes. Autopsy revealed the probable cause of death as hemorrhage.

RABBIT 8.—An albino female rabbit weighing 1.4 Kg. was operated on on Sept. 17, 1928. The operation was begun at 2:52 p. m. The adrenals were both removed intact without hemorrhage. The operation was completed, and the rabbit was returned to its cage at 3:21 p. m. apparently in good condition. It survived throughout the afternoon, but was found dead the following morning. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 10.—A piebald female rabbit weighing 1.1 Kg. was operated on on Sept. 17, 1928. The operation was commenced at 3:34 p. m. The adrenals were removed intact and without much hemorrhage. The rabbit was returned to its cage at 4:05 p. m. apparently in good condition. It survived the operation and was the first animal successfully doubly adrenalectomized and used in the series.

RABBIT 11.—An angora albino female rabbit weighing 1.6 Kg. was operated on on Sept. 17, 1928. The operation was commenced at 4:15 p. m. The adrenals were removed intact and without much hemorrhage. The operation was completed, and the animal was returned to its cage in apparently good condition at 4:58 p. m. It survived the afternoon, but was found dead the following morning. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 12.—An angora albino female rabbit weighing 1.3 Kg. was operated on on Sept. 18, 1928. The operation was begun at 1 p. m. The adrenals were removed readily and with relatively little hemorrhage. The operation was com-

pleted, and the animal was removed to its cage at 1:28 p. m. It survived the afternoon and the following morning until 11:30 a. m., at which time death occurred. Autopsy revealed no apparent cause for death (insufficiency?).

RABBIT 13.—A white female rabbit weighing 1.3 Kg. was operated on on Sept. 18, 1928. The operation was begun at 1:11 p. m. The adrenals were removed intact with little hemorrhage. The operation was completed, and the animal was removed to its cage at 1:29 p. m. in apparently good condition. It survived and was the second animal used in the experimental series.

RABBIT 14.—A white female rabbit weighing 1.5 Kg. was operated on on Sept. 18, 1928. The operation was started at 1:55 p. m. The adrenals were removed with some difficulty; the left gland was fragmented during removal, and considerable hemorrhage was encountered. The operation was completed, and the

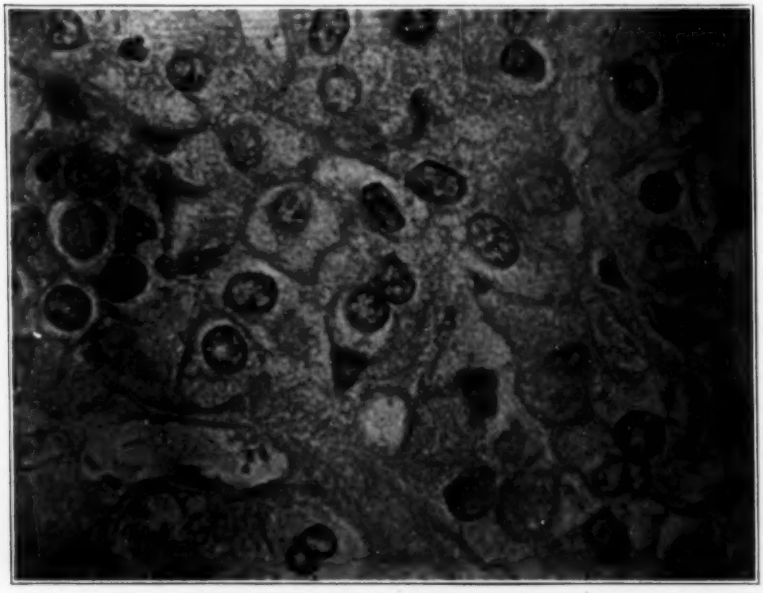

Fig. 4.—Normal adrenal medulla in the dog; high power photomicrograph.

rabbit was removed to its cage at 2:32 p. m. It survived the afternoon, but was found dead the following morning; autopsy showed the cause of death as hemorrhage.

RABBIT 15.—A brown female rabbit weighing 1.1 Kg. was operated on on Sept. 18, 1928. The operation was commenced at 2:50 p. m. Adrenalectomy was performed with little difficulty and with virtually no hemorrhage. The animal was returned to its cage at 3:12 p. m. in apparently good condition. Death occurred at 5:30 p. m.; at autopsy, no cause for death could be discovered (insufficiency?).

RABBIT 16.—A piebald female rabbit weighing 1 Kg. was operated on on Sept. 18, 1928. The operation was begun at 3:35 p. m. The adrenals were removed easily and with little hemorrhage. The animal was returned to its cage at 4 p. m. in apparently good condition. It survived the afternoon, but was found dead the following morning; autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 17.—A piebald male rabbit weighing 1.4 Kg. was operated on on Sept. 19, 1928. The operation was begun at 1:28 p. m. Adrenalectomy was performed with facility and without much hemorrhage. The animal was returned to its cage. It survived and was the third animal used in the experimental series.

RABBIT 18.—A white angora male rabbit weighing 1.2 Kg. was operated on on Sept. 19, 1928. The operation was commenced at 2:11 p. m. The adrenals were removed with some difficulty, both being fragmented and considerable hemorrhage being encountered. The operation was completed and the animal removed to its cage at 2:41 p. m. in relatively poor condition. It died at 4 p. m.; autopsy revealed the probable cause of death as hemorrhage.

RABBIT 19.—A white female rabbit weighing 1.5 Kg. was operated on on Sept. 19, 1928. The operation was begun at 2:45 p. m. Adrenalectomy was unusually easy and relatively little hemorrhage was encountered. The operation was completed, and the animal was removed to its cage at 3 p. m. in excellent condition. It survived the night, but died at 10 a. m. the following morning. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 20.—A piebald male rabbit weighing 1.3 Kg. was operated on on Sept. 19, 1928. The operation was begun at 3:05 p. m. The adrenals were removed intact without difficulty and without hemorrhage. The operation was completed, and the animal was removed to its cage at 3:20 p. m. It survived the operation and was the fourth animal used in the experimental series.

RABBIT 21.—A white female rabbit weighing 1 Kg. was operated on on Sept. 21, 1928. The operation was commenced at 2 p. m. The adrenals were removed with some difficulty but without much hemorrhage. The operation was completed at 2:35 p. m., and the animal was returned to its cage in fair condition. It died at 7 p. m.; autopsy revealed no apparent cause for death (insufficiency?).

RABBIT 22.—A white male rabbit weighing 1.5 Kg. was operated on on Sept. 21, 1928. The operation was begun at 2:51 p. m. The adrenals were removed intact with slight hemorrhage. The operation was completed, and the animal was removed to its cage at 3:15 p. m. in good condition. It survived and was the fifth animal used in the experimental series.

RABBIT 23.—A piebald female rabbit weighing 1.1 Kg. was operated on on Sept. 21, 1928. The operation was begun at 3:30 p. m. The adrenals were removed fairly easily but some hemorrhage resulted. The operation was completed at 3:50 p. m., and the animal was removed to its cage. It survived the afternoon, but was found dead the following morning; autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 24.—A white angora female rabbit weighing 1 Kg. was operated on on Sept. 21, 1928. The operation was begun at 4:11 p. m. The adrenals were removed with some difficulty and slight hemorrhage. The operation was completed at 4:31 p. m., and the animal was removed to its cage in fair condition. It died at 5 p. m. apparently of shock; autopsy failed to reveal the cause of death.

RABBIT 25.—A white female rabbit weighing 1.2 Kg. was operated on on Sept. 21, 1928. The operation was begun at 4:45 p. m. Adrenalectomy was difficult and both glands fragmented; there was considerable hemorrhage. The operation was completed, and the animal was removed to its cage at 5:10 p. m. It survived the afternoon, but was found dead the following morning. Autopsy failed to reveal the cause of death (insufficiency?).

RABBIT 26.—A brown male rabbit weighing 1.4 Kg. was operated on on Sept. 25, 1928. The operation was commenced at 2:25 p. m. Adrenalectomy was

accomplished fairly easily, and not much hemorrhage was encountered. The operation was completed at 2:40 p. m., and the animal was removed to its cage. It survived and was the sixth animal used in the experimental series.

THE OBSTRUCTION AND INJECTION SERIES: THE EXPERIMENT PROPER

I. RABBIT 27.—A white female rabbit weighing 1.2 Kg. was used.

Obstruction was produced on Oct. 7, 1928, at 1:15 p. m. The animal was killed on Oct. 9, at 2 p. m., at which time it appeared ill. In the evening, the entire small intestine was removed and from the mucosa and the contents a toxin was prepared, according to the method of Ellis.

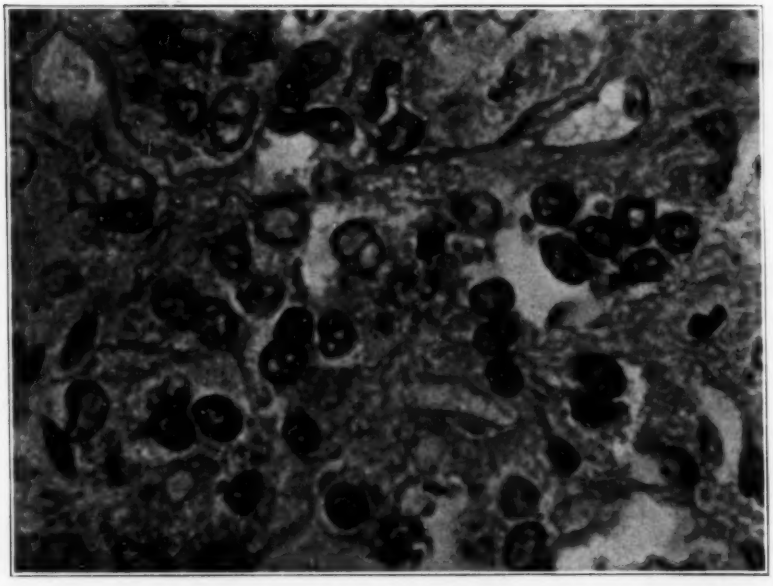

Fig. 5.—Adrenal medulla in the dog following the production of ileus; high power photomicrograph, showing pyknosis of nuclei and plasma cell infiltration.

RABBIT 33.—A brown female rabbit weighing 1.1 Kg. was used. The animal was healthy and normal.

RABBIT 10.—Adrenalectomy was performed on Sept. 17, 1928.

The toxin derived from rabbit 27 was divided into two equal parts (in this case 2.7 cc.); one part was injected into the normal rabbit 33, and the other into the adrenalectomized rabbit 10, at 3:15 p. m.

3:15 to 3:30 p. m.: Neither rabbit exhibited any particular symptoms except that both appeared disinclined to move about, and at the end of this period the healthy rabbit was found to have defecated several round, hard pellets.

3:30 to 4 p. m.: Both rabbits "drooped" considerably. The pupils of both were widely dilated, and the normal animal passed considerable quantities of fecal material which first was formed, though soft, but later became mucoid and watery; toward the last, tenesmus was prominent in this animal. The adrenalectomized animal did not defecate nor exhibit tenesmus; it appeared to have been much

less affected by the injection than the normal and was generally brighter and more attentive to its surroundings.

4 to 4:30 p. m.: During the early part of this period the normal animal looked as if it were about to succumb; it lay on its abdomen with legs stretched out before and behind, continued to purge at intervals, was quite apathetic to its surroundings, and was unable to stand or sit; tremors were noticed in the hind limbs but these did not persist. By the end of the period, however, it appeared much better and was beginning to pull up its legs in an attempt to get to its feet, although its efforts were unsuccessful. The adrenalectomized animal was able to sit up, but appeared sick. Both animals refused food, but toward the end of the period it appeared as if both would survive.

4:30 to 5 p. m.: There was little change in the appearance of either animal though both looked somewhat brighter and at the end of the period both were sitting up. It was decided to discontinue detailed observations at this time, and both were returned to their cages.

6 p. m.: The normal animal had apparently almost recovered; the adrenalectomized one was apathetic, but otherwise exhibited no particular symptoms.

7 p. m.: The normal animal had apparently fully recovered, though possibly was not as active as before the injection. The adrenalectomized animal was stretched out and dead.

The normal animal fully recovered.

Autopsy on the adrenalectomized animal revealed no gross lesions in any of the organs, with the single exception of the small intestine; here, in places, was some hyperemia, and the mucosa was reddened in patches. No adrenal tissue could be discovered after careful search.

II. RABBIT 28.—A piebald female rabbit weighing 1.4 Kg. was used. Obstruction was produced at 2 p. m., on Oct. 11, 1928, and the animal was returned to its cage in good condition. The animal was killed at 2 p. m. on October 13, and the contents and mucosa of the small intestine were used for the preparation of toxin according to the method of Ellis.

RABBIT 34.—A white female rabbit weighing 1.2 Kg. was used. The animal was healthy and normal.

RABBIT 13.—Adrenalectomy was performed on Sept. 18, 1928.

The toxin derived from rabbit 28 was divided into two equal parts (4 cc. each in this case); one part was injected into the normal animal and the other part into the adrenalectomized animal at 5 p. m., on Oct. 14, 1928.

5 to 5:15 p. m.: For the first five minutes neither rabbit appeared to experience any ill effect from the injection. However, at the end of this period the normal rabbit defecated a fairly large amount of normally formed stools, and also urinated. At 5:15, both animals were beginning to become somnolent; they sat huddled up with their eyes closed, and resisted any attempts to change their positions.

5:15 to 5:45 p. m.: During this period both rabbits progressively lost control of both hind legs, and the normal one was unable to bear his weight on his front paws. The normal rabbit purged violently; quantities of partially formed stools and, toward the last, very watery and mucoid motions were noted. The adrenalectomized animal passed a few formed fecal pellets. At 5:45 p. m., the normal rabbit was lying on his side with pupils widely dilated, apparently in a moribund condition. The adrenalectomized animal was in only a slightly better condition; it was able to struggle to maintain its position when disturbed, but could not roll onto his abdomen when turned on its side. Both animals presented slight tremors of the extremities.

5:45 to 6:45 p. m.: The adrenalectomized rabbit progressively became comatose, and died rather unexpectedly in convulsions at 6 p. m. The normal animal gradually regained the use of its limbs and was sitting up at 6:45 p. m.

The normal animal fully recovered.

Autopsy on the adrenalectomized animal revealed no gross lesions; examination of the region of the upper poles of the kidney revealed total absence of adrenal tissue.

III. RABBIT 29.—A white male rabbit weighing 1.5 Kg. was used. Obstruction was produced on Oct. 13 1928, at 3:15 p. m., and the animal was returned to its cage in good condition. The rabbit was killed at 4 p. m., on October 15, and toxin was prepared, as in previous cases.

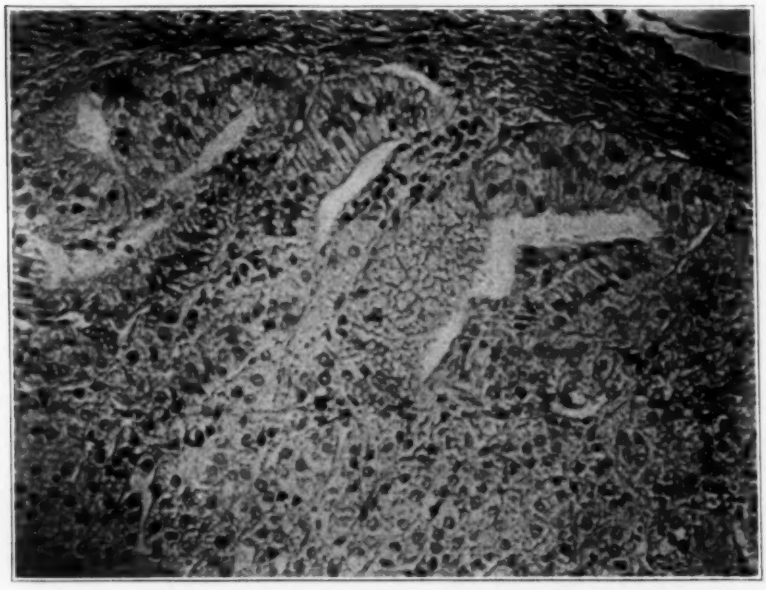

Fig. 6.—Adrenal cortex in the dog following the production of ileus; low power photomicrograph, showing areas of focal necrosis.

RABBIT 35.—A white male rabbit weighing 1.2 Kg. was used. The animal was normal and healthy.

RABBIT 17.—Adrenalectomy was performed on Sept. 19, 1928.

The toxin prepared from rabbit 29 was divided into two equal parts; one part was injected into the normal animal and the other into the adrenalectomized one at 2 p. m. on Oct. 16, 1928.

No special features were noted in this case except that the reaction to the injection was somewhat delayed beyond the intervals previously noted in the case of both rabbits, and neither animal appeared very ill at any time during the first two hours. Both rabbits were returned to their cages at the end of this period with the idea that probably the toxin was relatively inert. In the morning, however, the normal animal was apparently healthy, while the adrenalectomized one was dead. Rigor mortis had become established in the latter animal.

The normal animal survived indefinitely.

Autopsy on the adrenalectomized animal showed no gross lesions of any of the organs. No evidence of adrenal tissue could be found.

IV. RABBIT 30.—A white female rabbit weighing 1.4 Kg. was used. Obstruction was produced on Oct. 14, 1928 at 1 p. m. On October 16, the rabbit was killed and toxin was prepared as in the previous cases.

RABBIT 36.—A brown female rabbit weighing 1.2 Kg. was used. The animal was normal and healthy.

RABBIT 20.—Adrenalectomy was performed on Sept. 19, 1928.

The toxin derived from rabbit 30 was divided into two equal parts (5 cc. in this case); one part was injected into the normal rabbit and the other into the adrenalectomized animal at 2:15 p. m. on Oct. 17, 1928.

The results in this case almost exactly duplicate those reported in the previous case. Both rabbits showed little effect from the injection of the toxin, and were returned to their cages at the end of two hours; the normal animal survived indefinitely, but the adrenalectomized one was found dead on the following morning. The autopsy observations were insignificant except in demonstrating that all adrenal tissue had been removed.

V. RABBIT 31.—A white angora male rabbit weighing 1.3 Kg. was used. Obstruction was produced on Oct. 16, 1928, at 1:30 p. m., and the animal was returned to its cage in good condition. The rabbit was killed on October 18, at 2:25 p. m., and the toxin was prepared as previously.

RABBIT 37.—A piebald male rabbit weighing 1.4 Kg. was used. The animal was healthy and normal.

RABBIT 22.—Adrenalectomy was performed on Sept. 21, 1928.

The toxin derived from rabbit 31 was divided into two equal parts (2.5 cc. in this case); one part was injected into the normal rabbit and the other into the adrenalectomized animal on Oct. 19, 1928, at 3:10 p. m.

3:20 p. m.: The normal rabbit defecated a quantity of soft formed stools; it appeared sick and its respirations and pulse rate were rapid. The adrenalectomized animal was unaffected.

3:30 p. m. The normal animal was weak and had some difficulty in maintaining its balance; the adrenalectomized animal began to look sick.

3:40 p. m.: The normal rabbit had purged violently mucous and watery stools. The adrenalectomized animal had also defecated, but the movements were normal.

4 p. m.: Both rabbits had become so weak that they could no longer stand. The pupils of both were widely dilated; the skins of both were deeply cyanosed. Both exhibited fibrillary twitchings in the rear limbs.

5 p. m.: Both rabbits were in essentially the same condition as previously, except that paralysis was more marked in the adrenalectomized animal.

6 p. m.: Both rabbits were very sick, but the formerly normal one had apparently recovered somewhat. Both were placed in their cages for the night.

8 p. m.: The adrenalectomized animal died in violent convulsions. The normal animal had recovered somewhat.

Two cubic centimeters of blood was taken from the ear veins of both animals for chloride determination just prior to the injection of the toxin and a similar amount at the end of two hours for the same purpose. The chloride determinations showed: in the normal animal prior to injection, 528 mg. per hundred cubic centimeters, while two hours after injection it was 518 mg. per hundred cubic centimeters; in the adrenalectomized animal prior to injection, 445.5 mg. per hundred cubic centimeters, while two hours after injection the amount was the same.

The normal animal survived indefinitely.

Autopsy of the adrenalectomized animal showed absence of all adrenal tissue. No significant organic changes were found, with the exception of moderate distention of the small intestine which was filled with liquid yellow contents and a great deal of mucus.

VI. Rabbit 32.—A white female rabbit weighing 1.5 Kg. was used. Obstruction was produced on Oct. 19, 1928, at 4:20 p. m., and the animal returned to its cage in good condition. The rabbit was killed on October 21, at 5 p. m., and the toxin was prepared as previously.

Rabbit 38.—A piebald female rabbit weighing 1.2 Kg. The animal was healthy and normal.

Rabbit 26.—Adrenalectomy was performed on Sept. 25, 1928.

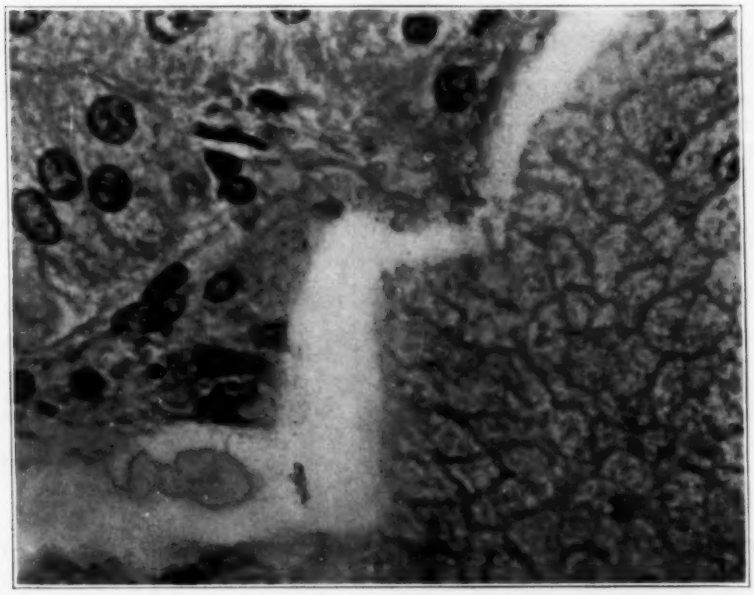

Fig. 7.—Adrenal cortex in the dog; high power photomicrograph of figure 6, showing pyknosis of nuclei and part of the area of focal necrosis.

The toxin derived from rabbit 32 was divided into two equal parts (3 cc. in this case); one part was injected into the normal (rabbit 38) the other into the adrenalectomized animal (rabbit 26) at 3:30 p. m. on Oct. 20, 1928.

No particular features of new interest were noted. Both rabbits experienced rather severe reactions within an hour; both became practically comatose in an hour and a half; they both exhibited some tenesmus, but the bowel movements of the normal rabbit were profuse and mucoid, while those of the adrenalectomized rabbit were scanty and formed, though soft and covered with mucus. Both animals were in apparently in extremis at the end of two hours. Two cubic centimeters of blood had been secured from the ear veins of both of the animals for a blood chloride determination just prior to the injection of the toxin. It had been decided to secure a similar amount at the end of two hours, in order that any possible decrease in chlorides might be detected. Both animals, however, were virtually

moribund at the end of two hours, as previously noted, and blood could not be secured from the veins of either animal. It was felt that neither animal could survive many minutes longer, and cardiac puncture was performed.

The adrenalectomized animal died during this procedure, possibly a cardiac death.

The normal animal recovered and survived indefinitely.

Autopsy on the adrenalectomized animal showed no adrenal tissue. The heart showed evidence of puncture, of course, but only a drop or two of blood was found in the pericardium.

The chloride determinations showed: in the normal rabbit before injection, 501.6 mg. per hundred cubic centimeters, and after injection, 495 mg. per hundred cubic centimeters; in the adrenalectomized rabbit before injection, 511.5 mg. per hundred cubic centimeters and after injection, 462 mg. per hundred cubic centimeters.

SUMMARY

Under as similar conditions as could well be devised six pairs of rabbits were injected with toxin chemically prepared, in as pure form as possible, from the mucosa and intestinal contents of other rabbits in which obstruction had been present for about forty-eight hours. Each pair of animals that had been given injections of toxin consisted of one rabbit which was healthy and normal, as far as could be determined, and an animal from which both adrenals had been completely removed approximately two or three weeks previously, and which had apparently completely recovered from the effects of the operation. Precisely the same dose of toxin was injected into both animals of each pair, the toxin from one animal with obstruction being divided for the purpose into two equal parts. The weight of the normal animal of each pair was selected so as never to exceed the weight of the adrenalectomized one, thus throwing any possible advantage in favor of the operated animal.

The results were conclusive. Both animals of each pair showed the symptoms of intoxication that have been previously reported by several investigators: weakness, tremors, dilated pupils, diarrhea and tenesmus. The normal rabbits invariably showed much more severe reactions than the adrenalectomized rabbits, and diarrhea with tenesmus was a prominent feature of the intoxication. The adrenalectomized animals showed the latter manifestations in very mild degree. While the animals of the normal series all survived indefinitely, though after a period of alarmingly severe reactions in most cases, the adrenalectomized rabbits all died within a period of twelve hours, in spite of the apparently relative mildness of their reactions.

Blood chloride determinations in two pairs of animals showed either no decrease at all or only slight decrease in chloride content during the two hour period following the injection of the toxin, and while the animal showing the greatest decrease was one from the adrenalectomized series and, accordingly, died, the animal showing the next greatest decrease was a normal animal and lived. Furthermore, the other adrenalectomized

animal showed no decrease, though it died, while the other normal animal showed no significant decrease yet lived.

It is accordingly believed that these experiments demonstrate that:

1. The lethal dose of toxin derived from the mucosa and intestinal contents of animals in which obstruction has been produced is much less for doubly adrenalectomized animals than for normal ones.

2. The adrenal glands evidently serve a definite function in combating a toxemia produced by the injection of toxin so derived.

3. The severity of the symptoms and signs of such a toxemia are a false guide to the prognosis in cases in which the adrenals cannot function.

COMMENT

The present series of experiments will have little interest for those who feel that the characteristic toxin which can be prepared, as previously described, from the contents and mucosa of loops of intestine proximal to an obstruction is an adventitious substance that ordinarily does not find its way into the circulation and therefore has no essential part in the production of the toxemia of ileus. On the other hand, granted that the reverse is true, and that the toxin under discussion probably does enter into the etiology of the symptom complex, a new and most fascinating sidelight is thrown on the problem of intestinal obstruction by the apparent incrimination of the adrenal glands as agents in a protective mechanism against the toxemia. Unfortunately, in spite of the fact that the adrenal glands have been known for years to subserve such a protective mechanism in the case of other toxic substances, organic and inorganic, no effective way of reinforcing this protective action in times of stress and strain has as yet been devised either through the isolation of an efficient and injectable extract of the adrenal gland of other animals or by measures designed to support the gland of the affected animal during the period in which it is called on to carry a load which it cannot bear unaided.

All the evidence at present available seems to indicate that the cortex of the adrenal gland and not the medulla is the tissue responsible for the protective mechanism, but attempts to utilize this fact in a practical way have apparently thus far met with failure. Such cortical extracts as have been prepared have been disappointingly inefficient, although emulsions of cortical tissue have been shown to detoxify at least one biologic toxin (Cobra venom, Meyers [23]), and autoplastic transplantation of the adrenal cortex has been shown to increase the resistance of animals previously lowered by adrenalectomy (Jaffe [24]).

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23. Meyers: Tr. Path. Soc. London, 1898.

24: Jaffe, H. L.: On Diminished Resistance Following Suprarenalectomy in the Rat and the Protection Afforded by Autoplastic Transplants; Am. J. Path. **2**:421, 1926.

On the basis of such fragmentary knowledge as is available at present, it seems probable that the influence of the adrenal cortex in combating intoxication is indirect rather than direct, and possibly a fairly complicated mechanism is involved. Perhaps the adrenals influence the general metabolism or the special metabolism of some intermediate tissue or they may control the usual mechanism of antibody production. In this connection the observation of Marine and Baumann is interesting—that the administration of physiologic solution of sodium chloride and Ringer's solution is of value in prolonging the life of those animals which ordinarily rather quickly succumb after double adrenalectomy, since the administration of sodium chloride is known to be of value in combating the toxemia of intestinal obstruction clinically.

From a clinical point of view it is believed that an appreciation of this protective function of the adrenal glands in intestinal obstruction is of the utmost importance. If, as seems to have been established histologically, these glands undergo degenerative changes in obstruction, it must be fairly obvious that treatment in order to be effective must be instituted early in intestinal obstruction, and such treatment must be aimed at the removal of toxic products from the obstructed loops of intestine before extensive degenerative changes have occurred in the adrenal cortices.

An amount of toxic absorption can be successfully combated by the body in the earlier stages when the adrenal mechanism is intact which would be rapidly and inevitably fatal once the cortical function has been seriously damaged.

Consequently, it would seem irrational to temporize very long with symptomatic treatment in any severe clinical case. The administration of spinal or splanchnic anesthesia in an attempt to relieve an adynamic ileus must be performed early and not as a last resort. In the early stages of obstruction the restoration of the motor function by any means will be effective, since the cortical protective mechanism is intact; later such restoration, though complete, may be just as hopelessly ineffective, since even though further absorption may be minimized or completely overcome, the protective mechanism may be unable to take care of the dose already absorbed.

In a similar way, enterostomy, to be effective, must be performed relatively early. It will almost inevitably allow the escape of only part of the toxic intestinal contents, and the condition of the cortical protective mechanism will determine whether the indivilual can successfully take care of the residuum or whether he will be overwhelmed thereby.

ACUTE COMPLETE OBSTRUCTION OF THE DUODENUM FOLLOWING A GASTROJEJUNOSTOMY

CURE BY DEGASTRO-ENTEROSTOMY *

JOHN E. SUMMERS, M.D.
OMAHA

The clinical fact has long been noted that the immediate seriousness of an acute intestinal obstruction depends on the location of the obstruction. When located in the duodenum, the higher the obstruction is below the opening through which the bile and pancreatic secretions are discharged, the more serious is the toxicity and the earlier the fatality. Numerous experimental occlusions of the duodenum have proved this.[1] Rapid fatalities follow obstructions in the small intestine, and the nearer the obstruction is located to the approach to the duodenum, the earlier death occurs. On the other hand, obstructions in the large bowel may exist for a considerable number of days before symptoms threatening life develop. Of course, if the obstructing cause, wherever located, so interferes with the vitality of the bowel that the blood supply is shut off, gangrene and peritonitis hasten the end. In such an instance, bacterial infection is overwhelmingly added to the causes of the commonly described toxemia. Not infrequently disorders of general health are noted in incomplete duodenal stenosis, most often located near the duodenojejunal junction.[2] However much one may agree or disagree with experimental physiologists [3] that the chief danger in acute intestinal obstruction is the loss of water and the inorganic constituents of the blood, there is, in my opinion, no question that safety for the sufferer consists primarily in draining the intestine. This, when done early, is accomplished by relieving the obstruction itself. When the patient is not seen until late, only temporizing measures are permissible, and the procedure of a simple drain introduced into the bowel above the obstruction is indicated. It has been proved experimentally and clinically that sodium chloride, when administered, has a positive effect in reducing the toxicity in intestinal obstruction. It is given intravenously, subcutaneously and by rectum, in large quantities of water. The water is

* Submitted for publication, March 5, 1929.

1. Duval, P.; Roux, J. C., and Béclère, H.: Études sur le duodénum, Paris, Masson & Cie, 1924.

2. Summers, J. E.: The Dilated Duodenum, Ann. Surg. **88**:576 (Sept.) 1928.

3. Discussion of symposium on Intestinal Obstruction, J. A. M. A. **91**:1592 (Nov. 24) 1928.

corrective of the dehydration. If one should await the corrective effects of the toxicity resulting from the intravenous administration of sodium chloride before establishing drainage above the obstruction, I fear it would be bad judgment. The acts of intestinal drainage, intravenous administration of large quantities of physiologic solution of sodium chloride and blood transfusion should go hand in hand—at least that is my experience.

In papers of my own [4] I have advocated the vital importance of draining the intestine above the obstruction, emptying the intestine through several incisions when practicable. Forgetting for the moment chloride depletion, Holden [5] has given the best corroborative evidence that the greatest danger of acute intestinal obstruction, wherever located, may be toxemia from absorption of the intestinal contents. Among his last fifty-one patients with acute intestinal obstruction on whom operations were performed, there were only three deaths, whereas, among a large number on whom operations were done before these his mortality rate was 50 per cent. He attributed his, probably to date unapproached, improved success to the fact that in each instance he practiced a method of emptying the imprisoned intestinal contents by a process of stripping, which caused almost complete emptying.

The foregoing digression from the subject of my clinical report seemed necessary because of the unusual opportunity afforded to discuss the dangers of delay, especially in high intestinal obstruction, as well as the possibilities of sustaining life by the measures advocated by physiologists.

REPORT OF A CASE

A well developed and well nourished man, aged 28, an intern, was admitted as a patient in the University Hospital on Aug. 28, 1927, with the diagnosis of acute appendicitis and duodenal ulcer.

History.—In 1917 had begun a spring and fall series of rather vague gastric discomforts which were relieved by sodium bicarbonate and the taking of food. These symptoms continued, but to a lesser degree, through the patient's premedical course. During the four years of the medical course there was again a feeling of distention and gnawing in the epigastrium about two or three hours after meals. It seemed to be aggravated by acid food and by periods of stress, mental and physical, but had practically no seasonal relationship. Fluoroscopic and roentgen examinations confirmed the clinical diagnosis of duodenal ulcer. The hospital record showed that the young man had the benefit of the modern recognized medical treatment for duodenal ulcer, and that in spite of carrying on his part of an active surgical service he led a relatively comfortable existence, provided he was careful of his diet.

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4. Summers, J. E.: Tr. Sect. Surg. & Anat. A. M. A., 1902; Med. Herald **25**:295, 1904; Tr. Am. Surg. Ass., 1920, p. 377; Nebraska M. J. **11**:335, 1926.

5. Holden, W. B.: Intestinal Obstruction: Survey of 135 Personal Cases, Arch. Surg. **13**:882 (Dec.) 1926.

The day previous to admission as a patient, he experienced colicky pain and cramps in the right lower quadrant, followed by nausea and vomiting. As there was no apparent urgency about the case—the only physical observations being some muscle spasm tenderness in the right lower quadrant—surgical intervention was delayed.

Operation.—On Sept. 5, 1927, with the patient under general anesthesia, a high right rectal incision exposed the stomach and an area of induration near the

Fig. 1.—Gastrojejunostomy invaginated into stomach; obstructing adhesions had been removed.

pylorus, 2 cm. in diameter, on the anterior duodenal wall. A posterior gastro-enterostomy was considered advisable. The cecum was found to be undescended and was held high up under the liver. The appendix contained several hard concretions. The gallbladder appeared normal. An appendectomy was done and a routine posterior gastro-enterostomy performed. The patient was returned from the operating room in good condition. Seven hundred cubic centimeters of

physiologic solution of sodium chloride was given by hypodermoclysis, and 2,000 cc. by proctoclysis.

Progress.—Nothing abnormal was noted on the day of operation or on the second postoperative day. On the third day, there was a burning sensation in the epigastrium. The patient complained of considerable cramplike pain in the right lower quadrant, which was relieved somewhat by a colon tube and enema. On September 9, the administration of liquid diet was begun. The pain in the right

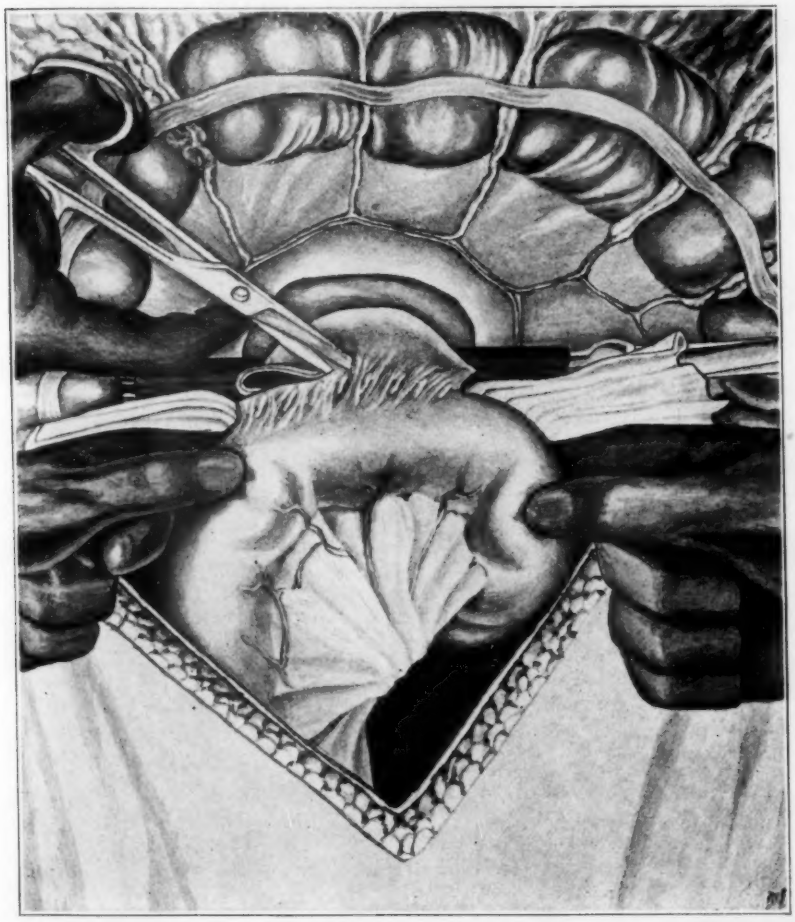

Fig. 2.—This and the following illustrations show steps in degastroenterostomy. Invagination is reduced. The gastrojejunostomy is released by sectioning of the stomach, leaving a narrow cuff of the stomach attached to the jejunum.

lower quadrant continued, and the patient complained of thirst. Gastric lavage and enemas gave little relief. On September 10 and 11, nothing noteworthy was observed. On September 12, pain in the right side became severe and was followed by nausea and vomiting. By gastric lavage only a small amount of greenish

mucus was washed out. Thirst was becoming marked. The following day, pain and epigastric burning persisted; lavage was still being used, but little relief was obtained. Proctoclysis, 1,500 cc. of physiologic solution of sodium chloride was instituted. On the afternoon of the eighth day burning in the epigastrium and pain in the right lower qudrant became more severe and rhythmical hiccups developed, occurring from every five to ten seconds. Hoffman's anodyne, atropine, camphor, amyl nitrite and morphine were all tried without avail. Gastric lavage (5 per

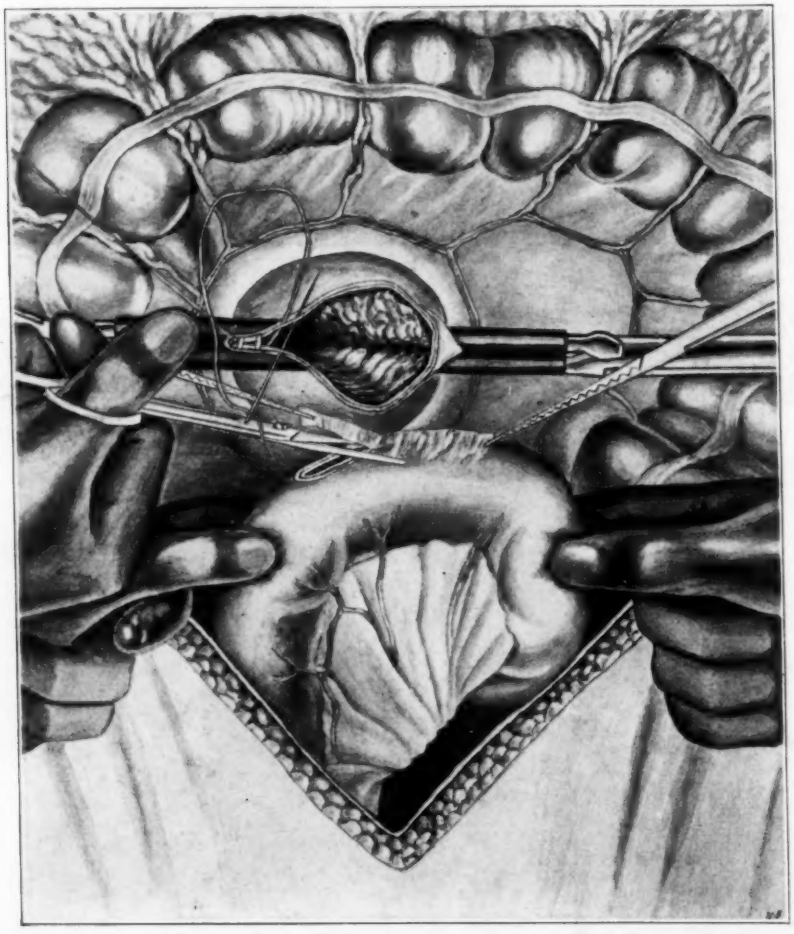

Fig. 3.—The upper part of the picture illustrates the suturing of the mucosa of the stomach; the lower part, the removal of the cuff of stomach from the jejunum.

cent soda) gave no relief. After thirty-six hours of singultus, the patient fell asleep. An enema given later returned slightly colored, with a small amount of hard, formed feces. No flatus was passed. The cramps recurred. Proctoclysis, 500 cc. of 10 per cent dextrose, was given together with 700 cc. of physiologic solution of sodium chloride by hypodermoclysis. A Levine nasal tube was passed,

and magnesium sulphate injected through the tube produced no results. An enema returned slightly colored.

The patient was almost too weak to talk above a whisper. On the tenth postoperative day, 750 cc. of matched citrated blood was given intravenously, together with 250 cc. of physiologic solution of sodium chloride. On the eleventh day, there was considerable twitching. He talked incoherently. Fluids given by mouth were not retained, so that 1,250 cc. of physiologic solution of sodium chloride was given intravenously. On the twelfth day, the Levine tube was again passed, and 150 cc. of a greenish fluid was aspirated. An enema returned clear. Through the Levine tube, barium meal was injected into the stomach. Careful observation with the fluoroscope for from fifteen to twenty minutes failed to

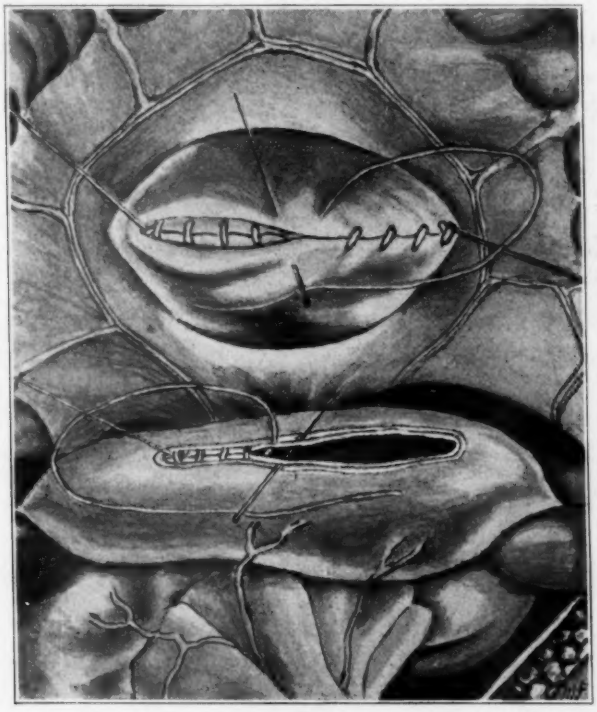

Fig. 4.—The upper part of the picture illustrates the mucosa of the stomach sutured; suturing muscularis and peritoneum. The lower part shows the suturing of the mucosa of the jejunum.

show any of the barium leaving the stomach. Another 750 cc. of matched citrated blood was given in the afternoon of the twelfth day, and was followed by some heat and itching.

Second Operation.—At 4:30 p. m. on the afternoon of the twelfth day, a second operation was performed. The old incision easily separated and spread open with little evidence of repair. A mass of dense adhesions was found in the area of the operative field. There was a herniation of the jejunostomy anastomosis into the stomach which caused complete obstruction of the duodenum and a few inches of the jejunum below the ligament of Treitz, and closed the gastro-

jejunostomy opening by compression. All of the tissues were densely adherent. The hernia was released and the anastomosis uncoupled. The stomach and jejunum were rapidly closed with double rows of chromic catgut, and the abdomen was closed with through and through silkworm gut sutures. During the operation, the pulse rate had jumped to 164 and the blood pressure dropped to 88 systolic; the diastolic pressure could not be determined. My much interested colleagues and assistants were so exercised, thinking the patient would die on the table, that after the stomach was closed I was urged to put a tube in the jejunum and get the patient to bed. Fortunately, I did not follow this advice. During the operation, 200 cc. of physiologic solution of sodium chloride with

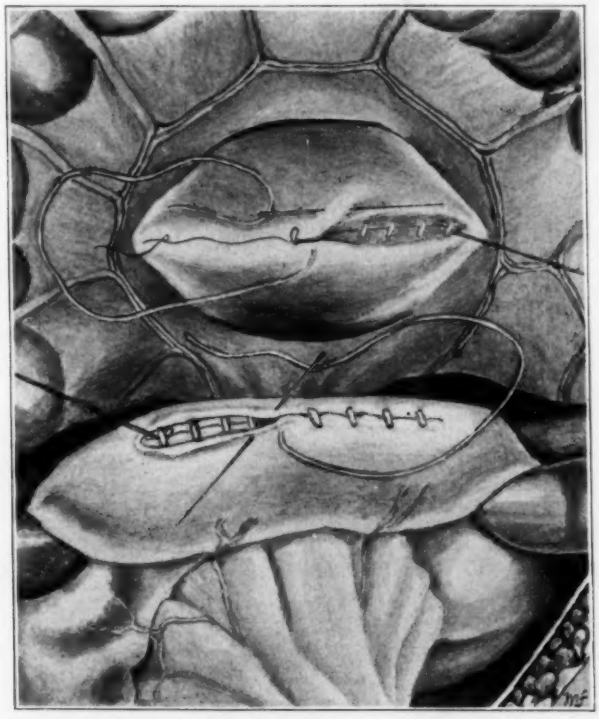

Fig. 5.—The upper part of the picture shows the burying of the suture line in the stomach by the Cushing right-angle continuous stitch; the lower part, the suturing of the muscularis and peritoneum of the jejunum.

10 minims (0.6 cc.) of epinephrine was given intravenously. The patient was returned from the operating room in an extreme state of shock; the body was cold and clammy, and the lips were cyanotic. The pulse could not be felt. Respiration had ceased. The foot of the bed was elevated, and a suction machine was used to remove mucus from the pharynx. A towel clip was put through the tongue to hold it forward and to aid in artificial respiration. Epinephrine, 10 minims, was given intravenously. The entire body was rubbed vigorously. Physiologic solution of sodium chloride with 20 minims (1.25 cc.) of epinephrine was given slowly by hypodermoclysis. After thirty minutes of artificial respiration, the apex beat could be guessed at 165 with the stethoscope. The respirations were

very shallow, but became more regular and full. Oxygen was administered; proctoclysis, with physiologic solution of sodium chloride, was begun. The patient was restless throughout the night. Just before operation a subnormal temperature had jumped to 103 F., the pulse rate to 164 and the respirations to 35. On the second day following, the temperature had dropped to 99.6 F., the pulse rate to 100, and the respirations to 20.

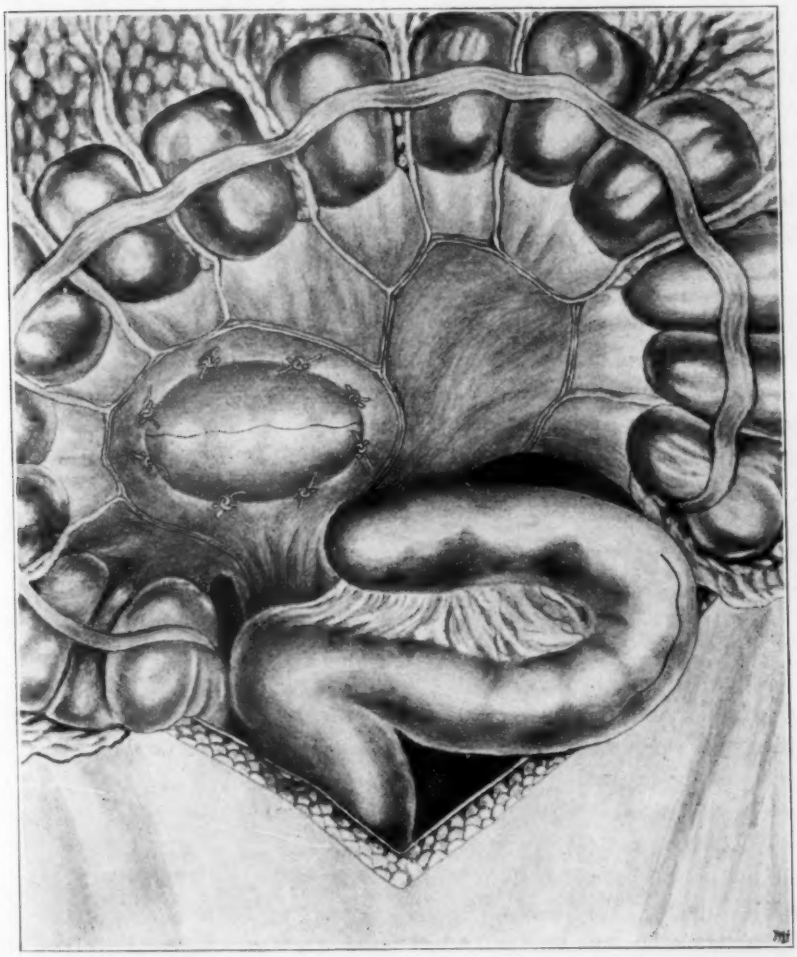

Fig. 6.—The stomach is fastened to the mesocolon by interrupted stitches. The wounds in the stomach and jejunum are closed.

Progress.—On September 19, 300 cc. of matched citrated blood was given intravenously, with 250 cc. of physiologic solution of sodium chloride about twenty-four hours after operation. Because of cramping and some nausea, gastric lavage with 2 per cent soda was given; this brought back some clear, dark-colored fluid. Abdominal pains were severe and were best controlled by heroin, which was the only narcotic to which the patient was reasonably susceptible. On September 20,

nausea persisted, but it was not so troublesome as before. There was a severe stomatitis, the result of dehydration. Air hunger was marked. One thousand two hundred cubic centimeters of physiologic solution of sodium chloride with 10 per cent dextrose was administered intravenously. On September 21, the cramps decreased, and the patient began to tolerate some fluids. Epigastric burning was relieved by sodium bicarbonate. On September 25, after ninety-six hours, some soft food was added to the liquids. On the eighth postoperative day, difficulty in swallowing was noted. There was pain underneath the sternum, radiating to the back. It was necessary to discontinue food and liquids for twenty-four hours and to limit the diet for the next three or four days in order to relax a probable cardiospasm. On October 10, the diet was gradually increased, and on the twelfth day the abdominal sutures were removed. Activities were renewed by degrees, and the patient was dismissed from the hospital in good condition on the nineteenth day following the second operation.

COMMENT

The delay in doing the second operation was due to two factors: 1. The patient objected to having anything done, being convinced that he was suffering from a dilated stomach. 2. There were too many physicians interested in the case, and no one was in command.

Since dismissal, or for the last one and a half years, the patient has remained on a soft, acid-free and roughage-free diet, and has not had many symptoms. The weight has returned to normal, and he has carried on his duties, feeling better than before the illness began. He is an active, hard-working man with a healthy appearance. X-ray pictures have demonstrated the stomach and duodenum functioning normally.

From the standpoint of animal experimentation, this man's life was saved from the intoxication of the duodenal block by the administration of large quantities of sodium chloride before and after the release of the obstruction. The symptoms exhibited in this case just before the second operation were not those commonly observed in cases of much lower intestinal obstruction when seen late. They resembled more those seen in infants with congenital pyloric stenosis—the neglected case. I once operated on one of these infants in the stage of convulsions —in fact, it had a convulsion while I was operating, and marvelously, the child lived.

Occasionally, it is necessary to release a gastrojejunostomy. I have employed a technic which when the urgency of the procedure admits is carried out as indicated in figures 1 to 6. Thalheimer [6] employed a somewhat similar method. It is different in that the closures in the stomach and jejunum are made at right angles to the long axes of the stomach and jejunum; the method of suturing is also different.

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6. Thalheimer, M.: J. de chir. **30**:385 (Oct.) 1927.

PERICARDOTOMY FOR PYOPERICARDIUM *

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When one considers the modern surgical optimism regarding the treatment for pyoperitoneum and pyothorax, the reluctance which has characterized surgical drainage of purulent exudate from the pericardial sac seems difficult to appreciate. In a masterly treatise on this subject, Winslow and Shipley [1] were able to collect only 118 recorded cases from the world's literature dealing with this subject.

Drainage of exudate contained in the pericardial sac was probably first suggested by Riolanus,[2] in 1648. It was not until 1855, however, that drainage of the pericardial sac through an opening in the sternum was first practiced by the Frenchman, Malle.[3] Larrey,[4] in 1829, first successfully employed the xiphocostal route. It remained for Hilsmann, in 1844, to cure a patient of pyopericardium by the performance of pericardotomy. Little attention was paid to the procedure until 1879, when the classic report of Rosenstein focused attention on the possibilities of the operation. More recently the successes of Winslow and Shipley and Peterson [5] should serve to popularize this relatively simple procedure; in the opinion of the former writers, operative treatment should yield about 70 per cent of cures.

The purposes of this paper are to discuss briefly the etiologic factors responsible for the disease and its diagnostic characteristics, to describe a recent experience and to outline a simple operative procedure.

In all probability, suppurative pericarditis never primarily arises in the pericardium. In most instances it represents an extension of some infectious process of the lung and pleura. Lobar (pneumococcus) pneumonia invariably extends to the pleura, producing an inevitable fibrinopurulent pleuritis. In many instances, pyothorax results and may involve the pericardium by contiguity. In many cases, the disease has followed perforating knife or bullet wounds with direct implantation

* Submitted for publication, April 4, 1929.

* From the Dayton Clinic.

1. Winslow, N., and Shipley, A. M.: Pericardotomy for Pyopericardium, Arch. Surg. **15**:317 (Sept.) 1927.

2. Riolanus, quoted by Hindenlang: Deutsches Arch. f. klin. Med. **24**:452, 1879.

3. Malle: Traité d'anatomie chirurgical et de médecine opérative, Paris, 1855, p. 888.

4. Larrey: Clin. Chir. **2**:303, 1829-1836.

5. Peterson, E. W.: Suppurative Pericarditis: Report of Three Cases, Arch. Surg. **16**:366 (Jan.) 1928.

of the infective agent. In other instances, the pyopericardium has been attributed to a local manifestation of a septicopyemia, such as that associated with osteomyelitis.

The failure to make a proper diagnosis of pyopericardium is so often revealed at the autopsy table that a brief recitation of the essential diagnostic criteria seems justified. The first requirement is the recognition of those diseases in which pyopericardium is a secondary manifestation.

FIG. 1.—Roentgenogram of chest showing greatly enlarged heart shadow and left pneumothorax.

If this is accompanied by a careful consideration of the history and physical examination, together with roentgenographic studies and diagnostic aspiration, the diagnosis should present no great difficulties. The most common physical signs are enlargement of the area of precordial dulness, frequently with shifting of the upper limit of dulness on changing the position, rapid pulse and respiration, muffled heart sounds, friction rub in the early stages and dull tympany over the infrascapular area. The difficulties encountered in distinguishing pyopericardium from car-

diac dilatation are indicated by the frequent performance of paracentesis cordis when parencentesis pericardii was being attempted. In simple dilatation the heart sounds are clear and sharp, whereas in pericardial effusions the sounds are distant and muffled.

REPORT OF CASE

B. L., a youth, aged 17, was first seen by Dr. P. A. Kemper, Germantown, Ohio, on April 12, 1928, when he complained of severe pain in the lower left side

FIG. 2.—Roentgenogram taken after aspiration of 925 cc. of turbid semipurulent fluid from pericardial sac, showing little decrease in size of heart shadow.

of the chest. He had a nonproductive cough, temperature of 102 F., pulse rate of 100 and increased respiratory rate. Physical examination revealed dulness over the lower half of the left side of the thorax. A diagnosis of lobar pneumonia was made. During the next five days, the symptoms and signs were aggravated. Ten days after the onset of illness, flatness was found on percussion, and drainage by the closed method yielded 1 liter of turbid straw-colored fluid during the first twelve hours. From April 22 until May 1, a moderate amount of exudate escaped, at the end of which time the patient experienced repeated chills and

sweats, dyspnea and cyanosis. On May 3, he complained of pain over the area of the liver. Dr. Kemper found considerable enlargement of the liver. At this time the heart sounds became more distant, the area of cardiac dulness became larger and the patient became orthopneic. The pain shifted to the interscapular region and increased as the area of cardiac dulness became larger.

On May 5, 1928, the patient was referred to me, with the diagnosis of left-sided lobar pneumonia, with empyema and purulent pericarditis. On admission to the Miami Valley Hospital, respirations were labored, even when he was in a sitting position; cyanosis was marked; the dulness around the liver extended

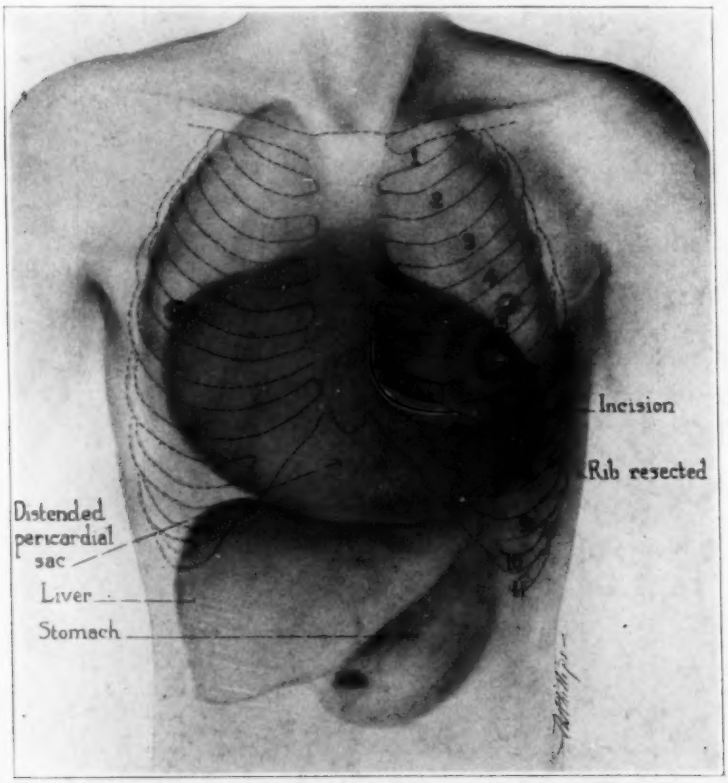

FIG. 3.—Drawing showing location of curvilinear incision along the left border of the sternum, beginning at the fifth left sternochondral junction and extending lateralward just below the inferior border of the sixth rib.

below the umbilicus; the superficial thoracic veins were greatly dilated; the heart sounds were distant and muffled; the area of cardiac dulness was greatly widened, and the legs were edematous. The temperature was 101 F., the pulse rate 120 and respirations 35. Flouroscopic examination and stereoscopic films of the chest (fig. 1) showed a heart shadow which occupied fully three fourths of the thoracic cavity, together with left pneumothorax.

On May 7, 925 cc. of turbid, semipurulent fluid was aspirated from the pericardial sac. This gave the patient temporary relief from his respiratory embar-

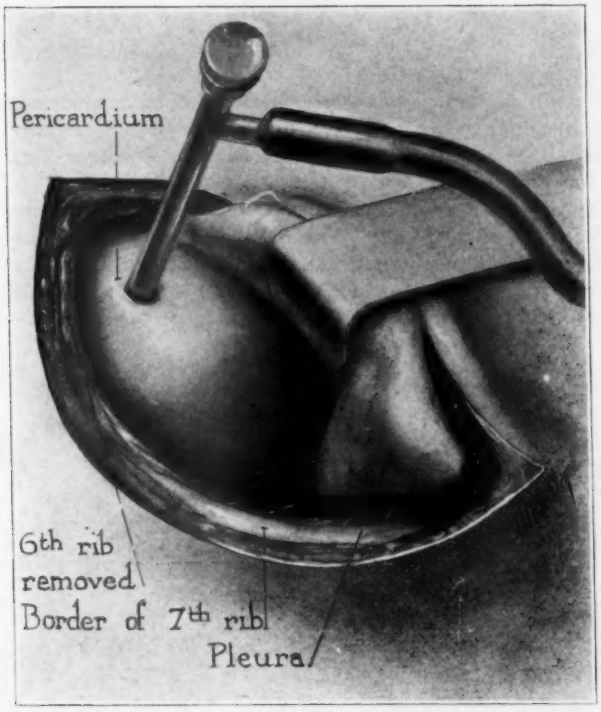

FIG. 4.—Drawing showing method of introduction of gallbladder trochar into pericardial sac.

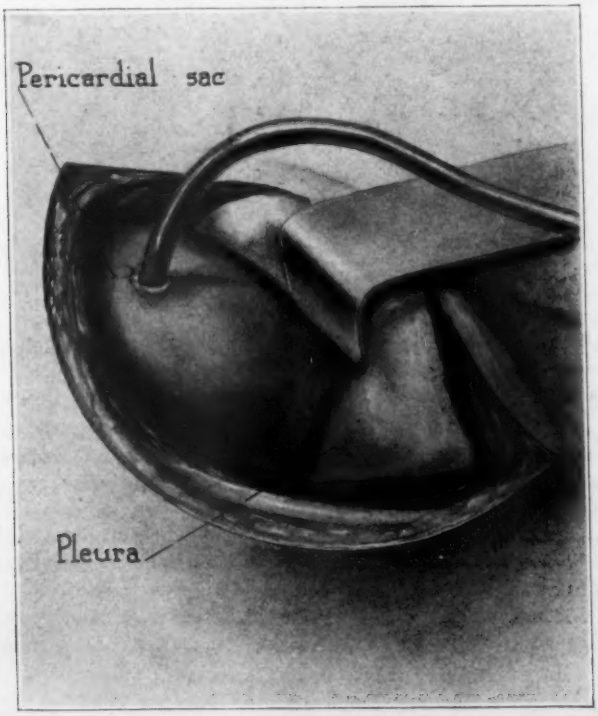

FIG. 5.—Drawing showing position of catheter fixed with purse-string suture.

rassment, but did not appreciably decrease the area of dulness around the heart (fig. 2). Pneumococci were recovered from the aspirated exudate. During the next twenty-four hours, the patient became obviously worse, and on May 9, pericardotomy was done under local anesthesia.

A curvilinear incision was made along the left border of the sternum, beginning at the fifth left sternochondral junction and extending lateralward just below the inferior border of the sixth rib to a point 2 cm. to the left of the costochondral junction (fig. 3). The flap was dissected upward from the underlying rib, exposing the costal cartilage of the sixth rib. The costal cartilage was removed.

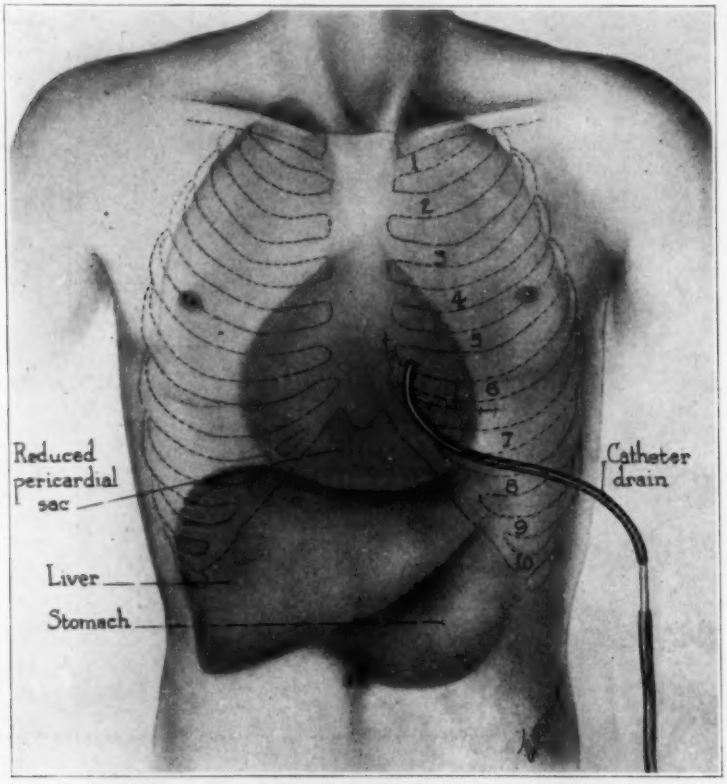

FIG. 6.—Drawing showing point of exit of catheter through stabwound in fifth intercostal space 1 inch above incision. The catheter is connected with a tube leading to a drainage bottle.

The pleura and lung were drawn lateralward by means of a broad retractor with a short hook. An aspirating needle attached to a Luer syringe was then introduced into the pericardial sac to determine the depth and location of the exudate. This was followed by the introduction of a gallbladder trochar into the sac (fig. 4). Approximately 600 cc. of thick purulent fluid escaped by gravity through the trochar and attached tube. A large Luer syringe was then attached to the free end of the tube and about 200 cc. of purulent fluid were withdrawn by suction. A purse-string suture was placed around the trochar, after which it was with-

drawn from the sac and a male catheter of similar caliber introduced and fixed with the purse-string suture (fig. 5).

The pericardial sac was then irrigated with 1 liter of physiologic solution of sodium chloride, at the end of which time the fluid returned clear. During the irrigation many large flakes of fibrin were washed out. The catheter was then drawn through a stab wound 1 inch (2.5 cm.) above the incision, near the sternum, and the wound was closed with interrupted sutures. The drainage tube was then connected with a tube leading into a large bottle containing antiseptic fluid (fig. 6).

The patient experienced immediate relief from the dyspnea and cyanosis, and the dependent edema rapidly diminished. The liver decreased in size and the

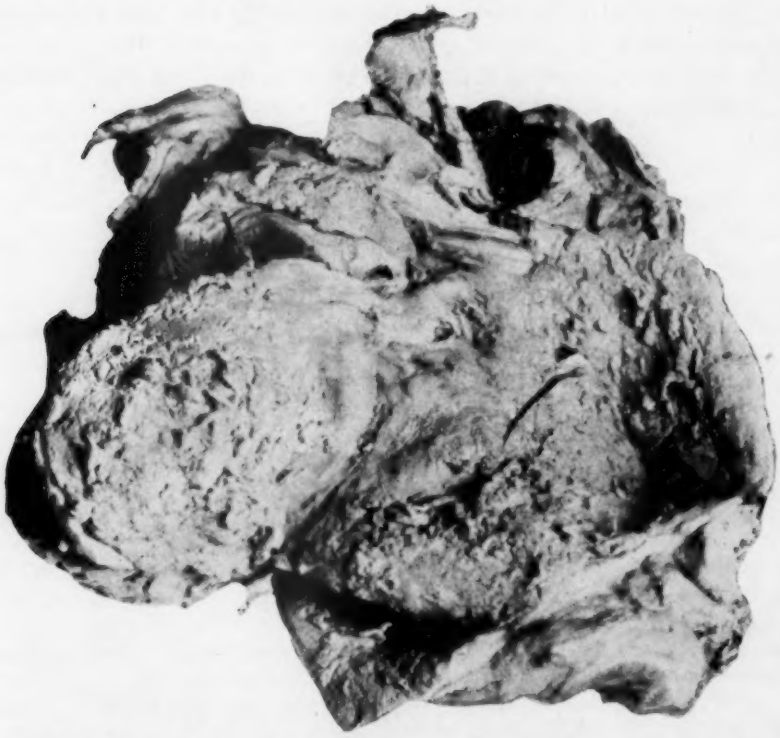

FIG. 7.—Heart showing typical fibrinopurulent pericarditis ("cor villosum" or "shaggy heart").

cardiac shadow returned to approximately normal. The lumen of the catheter was kept open by daily injections of sterile saline solution.

During the four days following the operation, the patient showed marked improvement. On the fifth day, however, he showed signs of overwhelming sepsis, and he died on May 16, one week after operation.

Postmortem examination revealed: left empyema (pneumococcus type); complete atelectasis and unresolved lobar pneumonia of the left lung; fibrinopurulent pericarditis ("cor villosum" or "shaggy heart") (fig. 7); organizing right-sided adhesive pleuritis; marked cloudy swelling, fatty degenerative infiltration and chronic passive congestion of liver, kidneys and myocardium; ascites of mild degree, and edema of the legs.

COMMENT

The immediate response to the simple operation was striking and gratifying. In view of the fact that the exudate which collects in the relatively small pericardial sac can find no physiologic outlet, it seems logical to contend that the early institution of surgical drainage offers to the patient his greatest hope. Two factors are in operation which constitute a serious handicap to the heart's work: first, the degenerative effects on the myocardium produced by the local inflammatory process; and second, the mechanical handicap produced by the rapidly increasing imprisoned exudate in the sac. Pericardotomy is a simple operation, presenting little or no risk, and is capable of saving life. The foregoing operative procedure is presented with the hope that it will stimulate others to give it a fair trial.

GANGLIONEUROMA OF MEDIASTINUM REQUIRING SURGICAL INTERVENTION FOR RELIEF OF OBSTRUCTIVE SYMPTOMS*

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Patients on whom it is possible to use only palliative surgical procedures are, unfortunately, often seen. Occasionally, the pathologic condition found gives rise to considerable discussion because of its relative infrequency.

Mediastinal tumors requiring surgical intervention because of symptoms of tracheal obstruction are rare. Of these, tumors arising from the sympathetic nervous system are perhaps the most rare. Because of its rarity and interest, we wish to report a case of ganglioneuroma apparently arising from the thoracic or the cervical segment of the sympathetic system.

REPORT OF A CASE

History.—A. B., a boy, aged 4 years, was admitted to St. Mary's Hospital on Nov. 20, 1925, with the complaint of difficulty in breathing and of swelling in the right side of the neck. The maternal grandfather was said to have died of cancer of the stomach and the paternal grandmother of cancer of the liver. A paternal uncle had died suddenly at the age of 6 months from an unknown cause. The boy was born on Oct. 22, 1921, delivery being normal. The mother did well and the child developed normally. No abnormality was noted in the other children in the family and there had been no serious diseases. The patient had had no headaches, pain in the chest, croup, gastro-intestinal disturbances or genito-urinary disease. Movements of the bowels were regular. He had a light attack of influenza in January, 1924, and contracted scarlet fever on March 1, the same year.

Three weeks after the onset of scarlet fever, or on March 22, a swelling was noted in the right anterior cervical triangle. The parents were assured that the condition was probably secondary to scarlet fever. The swelling persisted for nineteen months, but no symptoms developed until the latter part of October, 1925, when the patient had a severe cold, persistent cough, increasing hoarseness and pressure symptoms.

Examination.—The patient was a moderately nourished boy in considerable respiratory distress, as evidenced by cyanosis, stertor and voluntary respiratory efforts. There was a fulness in the right anterior triangle of the neck similar to that of a tuberculous adenitis. The left side of the neck was apparently normal. The right pupil was larger than the left, and the pupillary reflex was diminished. The tonsils were of the cryptic type, touching in the midline. On palpation of

* Submitted for publication, May 30, 1929.
* Read before the Western Surgical Association, Dec. 15, 1928.

the right side of the neck, there seemed to be two masses, each composed of lobules, rather firm, attached to the deep structures but not to the overlying skin. They were not tender. One mass extended from beneath the sternomastoid muscle toward the midline, while the other extended downward and was lost beneath the clavicle. Examination of the chest was unsatisfactory, owing to the respiratory noise.

Laboratory Observations.—On November 20, the urine was normal. The blood showed: red blood cells, 3,530,000; hemoglobin, 70 per cent (Dare); color index, 1; white blood cells, 5,500; polymorphonuclears, 65 per cent; small lymphocytes, 27 per cent, and transitionals, 8 per cent. The blood pressure was not taken. On Jan. 8, 1926, the blood showed: red blood cells, 2,500,000; hemoglobin, 52 per cent (Dare); white blood cells, 21,300; polymorphonuclears, 84 per cent; small lymphocytes, 9 per cent; transitionals, 5 per cent; polymorphonuclear eosinophils, 1 per cent, and polymorphonuclear basophils, 1 per cent.

Fig. 1.—Roentgenogram taken at the time of admission, showing a shadow in the right apex.

On Nov. 21, 1925, the roentgen report was: "There is a mass in the upper thorax which extends above the clavicle on the right side. The right border is well marked extending outward to the juncture of the middle and distal thirds of the clavicle and passing downward to the level of the fifth thoracic vertebra and rounding off toward the midline to be lost in the shadow of the spine. On the left, the border is not well marked, but the trachea is seen displaced somewhat to the left. This mass is smooth in outline and of uniform density. No changes of the bone are noted.

"Conclusion: This may be an abnormal thyroid; a thymus, or an 'hygroma.'"

Operation.—On the basis that the condition might possibly be an abnormal thymus, the patient was given four roentgen treatments, three over the upper thorax and one deep irradiation of the chest, but without appreciable benefit. On December 10, with the patient under an ether rausch, the tonsils and adenoids were removed in the hope that part of the respiratory obstruction might be relieved and as a preparatory step to a possible later operation on the neck. Section of the tissue

of the tonsil showed lymphoid hyperplasia and no other pathologic changes. On December 16, a second roentgen examination was made, concerning which the following report was made:

"Screen Examination: The cardiac shadow appears normal. There is a mass in the mediastinum extending down to the second interspace. It extends to the right displacing the right apex. Plate Examination: The cardiac shadow is normal; the bases are clear; there is an area of increased density involving the upper mediastinum from the level of the sixth dorsal vertebra upward. On the right it forms a curved line outward and upward obliterating the apex of the right lung and involving the neck above the clavicle. When compared with the previous x-ray there is no evidence of increase in size.

"Impression: Probable lymphosarcoma."

Fig. 2.—Ganglion cells distributed throughout section, many showing nuclei and nucleoli. Homogeneous supporting tissue. Note the tendency to grouping of the cells. Hematoxylin and eosin; × 157.

Course.—The patient was then temporarily discharged to recover from the tonsillectomy, and was readmitted on Jan. 6, 1926, at which time a roentgen examination showed a definite displacement of the trachea to the left at the level of the lower cervical and upper thoracic vertebrae. The patient's condition was pitiful—a typical picture of tracheal obstruction in an extreme form.

On January 9, an operation was done to relieve the tracheal obstruction, the various preoperative diagnoses recorded at that time being lymphosarcoma, lymphadenoma and thymoma. The gravity of the condition had been and was again fully explained to the parents, who were given to understand that we hoped for little more than temporary relief, and that a complete cure was out of the question.

A "T" shaped incision was made, one portion being parallel to the upper border of the clavicle and the other extending upward along the posterior margin of the sternomastoid muscle. A large mass of nodules was found deep in the neck,

intimately jointed with the right lobe of the thyroid and displacing the trachea to the left. This mass was removed and dissection carried downward underneath the clavicle, new growth being removed from about the common carotid artery and from above and beneath the subclavian vessels, and a mass of the growth was palpated in the mediastinum. It was impossible to determine the size or the extent of the growth. The incision was closed after a small roll rubber drain was placed at the lower point. Convalescence was rather slow and stormy but satisfactory in that the patient was completely relieved from dyspnea, which did not recur until a short time before death nearly eighteen months later.

On January 27, roentgen examination showed that the mass in the upper part of the right side of the chest was somewhat larger than on previous examinations. At the base of the right lung there was an area of increased density involving the lower third of the right lung field; this was more dense in the mesial half. There was a well marked, smooth, upper border suggesting either pneumonia, or a presence of fluid, but it may have been a metastatic growth.

The patient's temperature record showed marked variations. At the time of the first admission the temperature was normal and continued so, save for an occasional slight rise after roentgen therapy, until on December 4 when, without apparent cause, it began to rise, reaching 104 F. within twenty-four hours and dropping back to normal within forty-eight hours. Again after the tonsillectomy on December 10, there was a second similar febrile period, which subsided more slowly. At the time of the second admission, the temperature varied between 97.8 and 100.4 F. until after the operation on the neck, when it rose rapidly to 105 F. and was accompanied by a fine, general scarlatinal rash which was of not more than twenty-four hours' duration and was not followed by desquamation. The temperature, however, remained irregularly elevated for several days, subsiding gradually to normal for the first time on January 26, fifteen days after the operation.

After being discharged from the hospital, the patient was taken home, and letters from his parents reported him as playing actively and normally with his companions and being entirely relieved from his discomfort.

On May 16, 1926, he was again seen and appeared the picture of health. There was no palpable recurrence at the site of operation but percussion showed diminished resonance in the right apex. The report of the roentgen examination at that time was as follows:

"Plate examination of the chest shows a normal cardiac shadow. The diaphragm is normal in outline and the bases are clear. There is a definite shadow in the upper mediastinum which blends with the cardiac shadow. This increased density extends upward and to the right with a clearcut border and involves the right apex. There is also apparently an increased density in the neck on the right side. On the left the border of the heart blends with this mediastinal shadow which extends up to the level of the clavicle about 2 cm., to the left of the spine. When compared with the plate taken on Jan. 27, 1926, the shadow in the mediastinum shows no change. The increased density in the neck above the right clavicle is definitely less than it was at that time and the cloudiness at the right base has all disappeared.

"Conclusion: Tumor of the mediastinum."

The observations and the prognosis were again carefully explained to the parents, and permission, both verbal and written, was obtained for a necropsy when death occurred.

In June, 1926, the parents reported that they were putting the child in the care of a physician of another town who "treated by colored light." On April 2,

1927, the child was seen by Dr. Hagin and Dr. Gregory of Miller, S. D., who took a roentgenogram and confirmed our statement that the outlook was extremely grave, although stating that at that time the child's general condition was not acutely serious. They found a temperature of 100.4 F. and 13,000 leukocytes, and a blood smear showed some degeneration of the red corpuscles but no predominance of lymphocytes.

In May, 1927, the patient's condition began to decline, and on May 19 he was seen by Dr. C. E. Price of Orient, S. D. At that time the parents assured Dr. Price of permission for a necropsy. Shortly thereafter the patient developed a general edema, marked ascites and a recurrence of dyspnea. Death occurred at 6 p. m. on June 3, 1927. The parents absolutely refused a postmortem examination, which is greatly to be regretted, for study of the mass in the mediastinum and that in the area of the lung would have been most interesting and doubtless exceedingly instructive.

Pathologic Data.—Grossly, the material removed was of two kinds, one cellular and friable containing scattered yellowish pinpoint areas and the other grayish white, rather uniformly firm but elastic, each unit or nodule apparently having a thin covering or capsule. The former proved to be thyroid and the latter, neoplasm. On section, the tumor appeared to be made of a fine, closely interlacing structure which was grayish white and firm. A fibrous capsule was present and varied from 1 to 2 mm. in thickness.

The tumor was fixed in a diluted solution of formaldehyde, U. S. P. (1:10). It was embedded in paraffin from which sections were cut and stained with hematoxylin and eosin, van Gieson's stain, Orlandi's modification of Bielschowsky's silver method, thionin, Mallory's phosphotungstic acid and Weigert's myelin-sheath stains.

On microscopic examination, the tumor was fairly dense and consisted mainly of an interlacing fibrous framework supporting some nonmedullated nerve fibers. Ganglion cells were rather evenly distributed throughout the tumor mass. They usually occurred singly, though in places they were seen in groups (fig. 2). Most of these cells were mature, but they varied in size considerably. Some of them were multinucleated (fig. 3), each nucleus having a distinct nucleolus. In some of the cells, the nucleus appeared to be in a process of division while in others the nuclei were widely separated. The cytoplasm apparently was unaffected by the nuclear division. Nissl's granules were distributed throughout the cytoplasm (fig. 4), with a tendency to greater density about the periphery. Many of the cells were surrounded by a definite nucleated capsule. In sections stained by Orlandi's silver impregnation method, definite dendritic processes could be seen to come from the cells (figs. 5 and 6). These processes forked at varying distances from the cell. Many of the cells had undergone cystic degenerative changes (fig. 3).

In no section examined were there "rosets" or undifferentiated cells suggesting neuroblasts which are occasionally associated with ganglioneuromas.

ORIGIN OF GANGLIONEUROMA

Perhaps the outstanding paper in English on the subject of neuroblastoma and ganglioneuroma is that by Wahl,[1] who gave a concise but thorough review of the literature to 1914. We have drawn freely

1. Wahl, H. R.: Neuroblastoma: With a Study of a Case Illustrating the Three Types that Arise from the Sympathetic System, J. M. Research **30**:205, 1914.

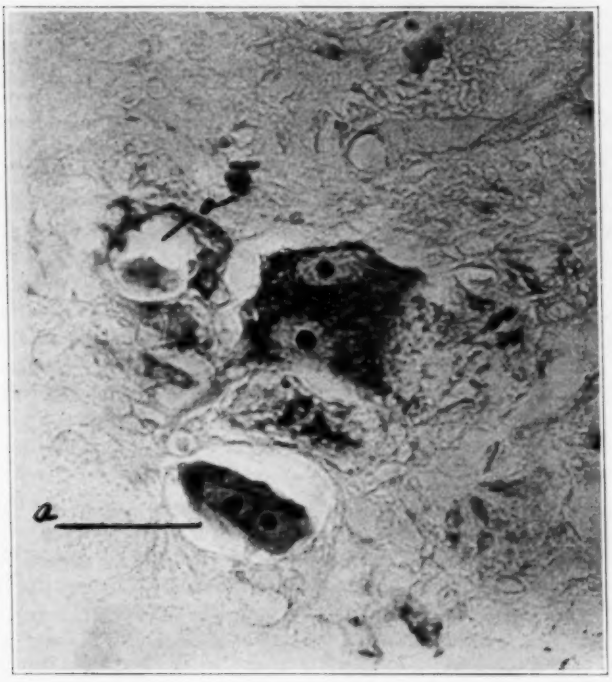


Fig. 3.—Multinucleated ganglion cells with Nissl's granules. Note the characteristic nuclei and nucleoli. Tendency for cystic degeneration of these cells (*a*). Thionin; × 450.

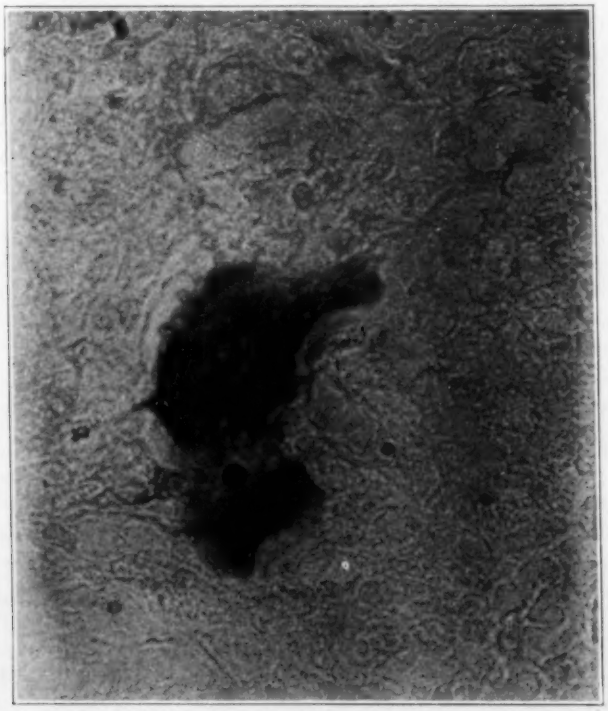


Fig. 4.—Ganglion cell with single nucleus and a distinct nucleolus. Note the Nissl granules. Thionin; × 1,000.

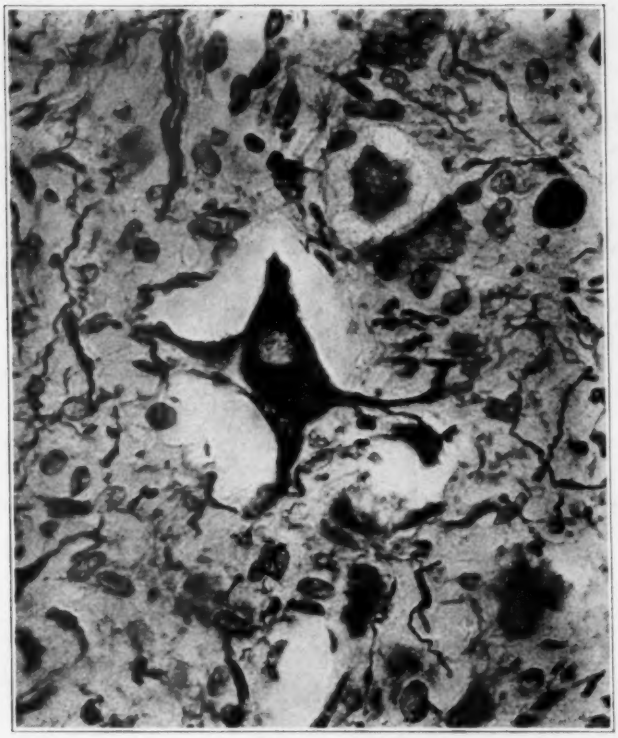


Fig. 5.—Ganglion cell with multiple dendrites, one of which divides some distance from the cell. Orlandi; × 450.

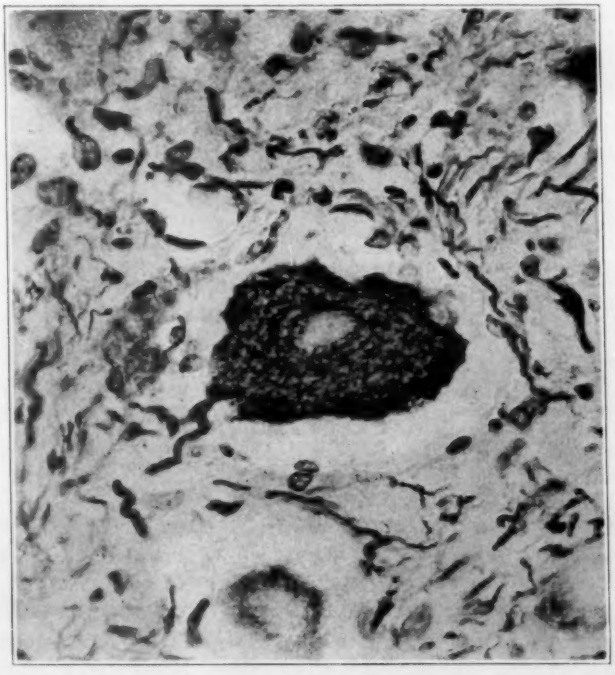


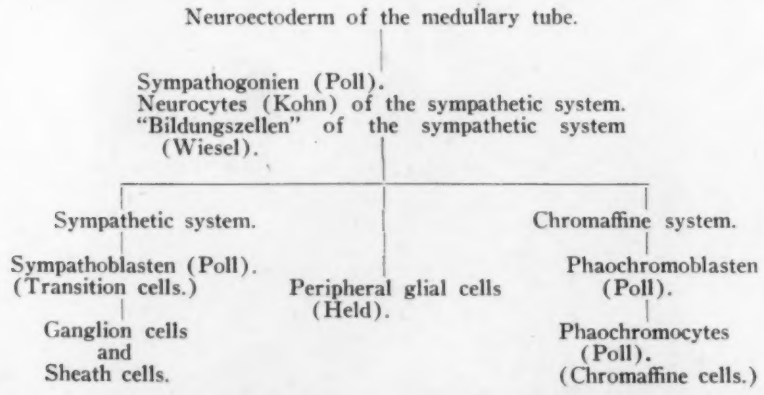
Fig. 6.—Ganglion cell showing a dendritic process which divides shortly after leaving the cell. Orlandi; × 450.

on this paper for information in making a study of our case. He pointed out, in the light of Kohn's work on the development of the sympathetic system, that "The embryonic sympathetic cells are not migrating preformed ganglion cells but are simple neurocytes formed in situ that have, locally, a different power of differentiation from elsewhere, in that they become differentiated on the one hand to ganglion cells, capsule cells, nerve fibers, and sheath cells and even glial cells, and on the other hand, to the chromaffine cells."

Simply stated, tumors of the sympathetic system arise from a cell rest, a mother cell called the neurocyte which has multipotential characteristics. The type or types of cells which characterize a tumor arising from the sympathetic nervous system depend, therefore, on the degree of differentiation to which the cells composing it have progressed.

CLASSIFICATION

Tumors arising from the sympathetic nervous system are divided into three main groups: (1) the neuroblastoma, (2) the ganglioneuroma and (3) the paraganglioma. The neuroblastoma is composed of undifferentiated cells and is malignant. These cells resemble lymphoid cells and are frequently arranged in rosets. The ganglioneuroma and paraganglioma are composed of highly differentiated cells and are benign. The former consists chiefly of ganglion cells, while the latter consists of cells having great affinity for the chrome salts similar to those of the medulla of the suprarenal gland. Between the undifferentiated cells of the neuroblastoma and the fully differentiated cells of the ganglioneuroma and paraganglioma there are cells in various stages of transition known as transitional cells. The genetic relation of the different nerve elements of which such tumors are composed is clearly expressed in the following scheme taken from Wahl.[1]



This genetic relationship makes it easy to understand the varied histologic picture which is frequently encountered in a single tumor.

Two or more nerve elements frequently have been observed in a single case, and in the case presented by Wahl all three types of tumor were present.

A girl, aged 2½ years, was markedly anemic and had had abdominal symptoms for several months, with irregular temperature, abdominal distention and enlargement of the inguinal lymph nodes. On examination, an irregular firm and fixed mass was found in the umbilical region. The postmortem observations as they pertain to this case were: malignant neuroblastoma of the sympathetic system arising in the left suprarenal gland and celiac plexus with metastasis to the liver, lymph glands, kidneys and left suprarenal gland; ganglioneuroma and paraganglioma of the left suprarenal gland.

To indicate the occurrence of two or more types of cells in a tumor, Robertson,[2] in 1915, suggested a fourth group. In this group, he placed tumors of group 1 in combination with either group 2 or 3, or both. For example, the tumor in Wahl's case would be designated ganglioparaganglioneuroblastoma and would be placed in group 4.

In the same year, Dunn[3] reviewed the literature on the subject and grouped the tumors according to the region from which they had arisen He collected fifty-one cases, the tumors of which had taken their origin in the following regions: four in the cervical segment, five in the thoracic segment, nineteen in the abdominal segment, eleven in the suprarenal gland, two in the subcutaneous tissue, four in the central nervous system and six in the peripheral nerves.

Reports of about sixty-five cases of ganglioneuroma are now recorded in the literature. Of this number, there are six cases which apparently have arisen intrathoracically; there are three cases, including ours, which have involved both the neck and the thorax and there are three cases which have been reported as arising in the neck (tables 1 and 2).

Loretz[4] is credited with having given the first description of ganglioneuroma and, incidentally, of one of the cases of intrathoracic ganglioneuromas:

A woman, aged 35, was found unconscious and in convulsions. She died the same day, and at autopsy, a smooth subpleural tumor, 7.5 by 4.5 by 4.5 cm., was found in the left thoracic cavity in the region of the second and third thoracic vertebrae. Grossly it was composed of two layers. The outer layer was light and consisted of fibrous tissue, blood vessels and fatty tissue. The central layer was more grayish and softer, resembling a section of the uterus. It consisted mainly of nonmyelinated nerve fibers in which there were rather typical ganglion cells.

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2. Robertson, H. E.: Das Ganglioneuroblastom, ein besonderer Typus im System der Neurome, Virchows Arch. f. path. Anat. **220**:147, 1915.

3. Dunn, J. S.: Neuroblastoma and Ganglioneuroma of the Suprarenal Body, J. Path. & Bact. **19**:456, 1914-1915.

4. Loretz, W.: Ein Fall von gangliösem Neurom (Gangliom), Virchows Arch. f. path. Anat. **49**:435, 1870.

The case reported by Martius [5] closely resembles the one reported by us and is worthy of being recorded here:

A boy, aged 2½ years, had a tumor in the right side of the neck which displaced and compressed the trachea. He was operated on because of dyspnea. At operation, the tumor was found intimately associated with the right lobe of

TABLE 1.—*Intrathoracic Ganglioneuroma*

No.	Author	Year	Sex	Age	Site	Size
1	Loretz, W.: Virchows Arch. f. path. Anat. **49**: 435, 1870	1870	F	35	Left thorax; second and third dorsal vertebrae	7 by 4.5 by 4.5 cm.
2	Borst, M.: Die Lehre von den Geschwülsten. Munich, J. F. Bergmann, 1902, vol. 1, p. 241	1902	?	?	Left subpleural	Child's head
3	Rindfleish, E.: Quoted by Borst	1902	?	?	Angle of wall of rib and anterior circumference of spine	?
4	Benda, C.: Verhandl. d. deutsch. path. Gesellsch. **7**: 265, 1904	1904	?	Child	Right side of neck and thorax	Apple
5	Friedrich, J.: Frankfurt. Ztschr. f. Path. **10**: 456, 1912	1912	F	73	Sixth to eighth right thoracic vertebrae	7 by 2.8 cm.
6	Martius, K.: Frankfurt. Ztschr. f. Path. **12**: 442, 1913	1913	M	2½	Right side of neck and thorax	3.5 by 2 by 0.75 cm.
7	Tschistowitsch, F. J.: Zentralbl. f. Chir. **35**: 576, 108	1908	F	12	Fourth to sixth right thoracic vertebrae	Goose egg
8	Brunner, A.: Arch f. klin. Chir. **120**: 364, 1924	1924	F	19	Second to ninth dorsal vertebrae; left thorax	17 by 12 by 8 cm.
9	Riggs and Good	1928	M	4	Mediastinum and right side of neck	Not determinable

TABLE 2.—*Ganglioneuroma Arising in the Neck*

No.	Author	Year	Sex	Age	Site	Size
1	Glinski, S. K.: Deutsche med. Wchnschr. **32**: 2044, 1906	1906	?	10	Deep in left side of neck	9 by 6.5 cm.
2	Woods, C. S.: Deutsche med. Wchnschr. **32**: 2044, 1906	1906	M	32	Right carotid sheath	9 by 8 by 4 cm.
3	Freund, P.: Frankfurt. Ztschr. f. Path. **13**: 266, 1913	1913	M	5¾	Right side of neck	9 by 6 by 4 cm.

the thyroid from which it was thought to arise. The patient died a short time later. At autopsy, two masses of tumor were found. One was nodular and extended from the right side of the thymus downward and medially to the right atrium, and surrounded the superior vena cava and main bronchus. This tumor mass contained undifferentiated and partly differentiated cells and was malignant. To the side and below, and somewhat separated from this mass, was a tumor

5. Martius, K.: Maligner Sympathoblastentumor des Halssympathikus teilweise ausdifferenziert zu gutartigem Ganglioneurom, Frankfurt. Ztschr. f. Path. **12**:442, 1913.

occupying the angle formed by the first and second ribs with the spine. It was 3.5 by 2 by 0.75 cm., smooth and firm and resembled a myoma. The tumor was composed of well differentiated ganglion cells and nonmedullated nerve fibers. It was considered benign. It was thought that the two masses of tumor had a common origin in the sympathetic nervous system, and that they differed only in degree of differentiation. As the sympathetic system from the midcervical to the first thoracic was intimately involved in the tumor, it was considered to have arisen in this region.

In 1924, Brunner [6] reported a case:

A girl, aged 19, for a period of two months previous to coming under his care, had had oppressive pain in the back and left side when lying down. Because of the pain, she could lie down only half an hour at a time. She obtained immediate relief on sitting up. Various diagnoses had been made, the final one being intrathoracic dermoid cyst. On examination, the patient was found to be of medium size. From the upper border of the scapula down to about the tenth dorsal vertebra there was almost complete dulness, and over which the breath sounds were diminished.

Roentgen and fluoroscopic examination showed a nonpulsile shadow, the size of a child's head, extending from the second to the ninth dorsal vertebra on the left. It was in close relationship to the spine. The anterior mediastinum was clear.

The patient was operated on by Sauerbruch. A paravertebral incision was made, and several ribs were resected over the mass. Exploration revealed a smooth, firm, round tumor slightly adherent to the pleura and markedly adherent around the aorta. The tumor arose from the posterior mediastinum, pushing the lung ahead of it. No attempt was made to remove the tumor at this stage. The cut edges of the pleura, however, were stitched to the tumor mass. At a later date, a second stage operation was done, at which time the tumor was removed with great difficulty. The patient had a stormy convalescence, developing a sterile empyema and finally a necrosis of the left lung which sloughed away entirely. This was thought to have been due to tying of the bronchial artery at the time of the operation. Several operations were done to relieve the symptoms arising from the complications. Incidentally, the patient developed club fingers, but the author pointed out that this was due not to the tumor but to the complications in the lungs.

The gross specimen measured 17 by 12 by 8 cm. and was lobulated. The surface of the cut section had a silky sheen and was grayish white. The tumor had a definite capsule, and connective tissue septums could be seen.

Microscopically, the tumor was composed of nerve fibers, the nonmedullated variety predominating, in which there were collections of rather normal-appearing ganglion cells. Some of them, however, had undergone cystic degeneration. The whole was supported by a structure of wide-meshed connective tissue.

Ganglioneuromas arising in the cervical segment have been removed surgically in two cases, those reported by Glinski [7] and Freund.[8]

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6. Brunner, A.: Die erfolgreiche operative Entfernung eines grossen Ganglioneuroms des hintern Mittelfellraumes, Arch. f. klin. Chir. **129**:364, 1924.

7. Glinski, S. K.: Ganglioneurom, abstr., Deutsche med. Wchnschr. **32**:2044, 1906.

8. Freund, P.: Ein Ganglioneurom des rechten Hals-sympathikus, Frankfurt. Ztschr. f. Path. **13**:266, 1913.

Freund's case was that of a boy about 6 years of age who had had a tumor in the right side of the neck for a year. He developed dyspnea three days before admission to the hospital. Operations in both instances were apparently successful.

SUMMARY

A case of ganglioneuroma arising from the thoracic or the cervical segments of the sympathetic system is reported.

The patient was a boy 4 years of age. The duration of the tumor was twenty-two months; that of the acute symptoms, three months. Operation was performed for relief of the tracheal obstruction; the complete removal of the growth was not possible. Complete relief was obtained for sixteen months. Death followed one month after the recurrence of symptoms.

Pathologically, the tumor showed typical ganglion cells in a bed of nonmedullated nerve fibers, some ganglion cells showing cystic degeneration.

VARIATIONS IN THE EXTRAHEPATIC BILIARY TRACT *

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The frequent recourse to surgery for disturbances in the function of the extrahepatic biliary tract makes imperative exact knowledge not only of the normal distribution of the bile ducts but of the variations occasionally encountered in this system.

The literature contains frequent references to this fact, and many cases are reported of injuries to the biliary tract during operation on subjects in whom the arrangement of the bile ducts was atypical. Jacobson [1] reported a case in which he severed the common bile duct during an operation for gallstones, because the cystic duct paralleled the hepatic duct for some distance. Many instances of similar accidents have been reported. Werelius [2] and Ginsburg and Speese [3] reported cases in which transection of the common duct had been caused entirely by an anomalous arrangement of the ducts. Stetten [4] reported a case in which the hepatic duct was divided instead of the cystic duct because of the parallel arrangement of the two.

Ruge [5] described the various forms of the biliary tract and classified them under three main types. The first type consisted solely of the normal angular mode of union of the cystic duct with the hepatic duct. The second type of anomaly included those in which the cystic duct paralleled, for a certain distance, the choledochus. The third type included the two arrangements of the cystic duct in which, instead of leading directly into the right side of the hepatic duct, it wound around it, either anteriorly or posteriorly. Eisendrath [6] (1918 and 1920)

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* Submitted for publication, Oct. 16, 1928.
* Work done in the Department of Pathology, University of Oregon.

1. Jacobson, J. H.: Repair and Reconstruction of the Bile Ducts, Am. J. Obst. & Gynec. **70**:940, 1914.

2. Werelius, Axel: Accidental Surgical Injuries to the Bile Ducts with Report of a Case, J. A. M. A. **68**:1545 (May 26) 1917.

3. Ginsburg, Nathaniel; and Speese, John: Autogenous Fascial Reconstruction of the Bile Duct, Ann. Surg. **65**:79, 1917.

4. Stetten, De W.: Anomalous Relations of the Cystic Duct or Gallbladder to the Hepatic Duct, S. Clin. North America **3**:539, 1923.

5. Ruge, Ernst: Beitrage zur chirurgischen Anatomie der grossen Gallenwege, Arch. f. klin. Chir. **87**:47, 1908.

6. Eisendrath, D. N.: Anomalies of Bile Ducts and Blood Vessels as the Cause of Accidents in Biliary Surgery, J. A. M. A. **71**:864 (Sept. 14) 1918; The Clinical Importance of Anatomical Anomalies in Biliary Surgery, Boston M. & S. J. **182**:573, 1920.

presented a study of 100 cases in which the variations in the biliary tract and their relations to the vascular system were discussed. He described each type of variation and specifically stated its significance in relation to accidents during operation. Flint [7] described two cases, noted clinically, of variations in the distribution of the biliary tract. In one, an accessory cystic duct was encountered during operation for gallstones; in the other, in which operation for cholecystitis was carried out, the cystic duct paralleled the choledochus for its entire length and emptied directly and independently into the duodenum. In an embryologic and comparative study of aberrant biliary vesicles in man and other mammals, Boyden [8] presented valuable data concerning the frequency with which duplication of the gallbladder may be encountered. In studies on 10,000 domestic animals and reports on 19,000 cadavers and patients in hospitals, the incidence varies somewhat as follows: once in 8 cats; once in 28 calves; once in 85 sheep; once in 198 pigs, and once in from 3,000 to 4,000 human beings. Accordingly, such duplication of the biliary vesicle appears to be relatively rare in man.

A variation from the usual distribution of the biliary ducts, however, is common. Therefore, since cholecystectomy is now more common than simple drainage of the gallbladder, a clear understanding of the more common variations in the distribution of the bile ducts is imperative.

DATA OBTAINED DURING DISSECTION OF CADAVERS

In this report, I wish to present the data which were accumulated during careful dissections of fifty-seven cadavers. The material for these dissections was obtained from necropsies performed for the coroner in Portland, Oregon, and the study was made in the laboratories of the Department of Pathology, the University of Oregon Medical School.

The extrahepatic tracts of the fifty-seven subjects which came under my observation in this study fall into four rather distinct groups. I was able to demonstrate the three types of distribution as described by Ruge and in general to confirm his observations as to the frequency of these variations. The first group of cases, those in which the angular mode of union maintains between the cystic and hepatic ducts constituted 58 per cent of all the dissections (fig. 1 *a*).

I have subdivided Ruge's second group of variations, those in which the cystic duct coursed parallel to the common bile duct, by arbitrarily

7. Flint, E. R.: Gallstones Associated with Anomaly or Injury of Bile Ducts, Brit. M. J. **1**:995, 1924.

8. Boyden, E. A.: The Accessory Gallbladder; an Embryological and Comparative Study of Aberrant Biliary Vesicles Occurring in Man and the Domestic Mammals, Am. J. Anat. **38**:177, 1926.

classifying the cystic ducts into two groups on the basis of their length. Furthermore, although the two ducts concerned are bound together in a fibrous union, their lumens are separate. Therefore, it seems better to speak of the cystic duct as running parallel to the hepatic duct and not to the common duct. I have designated the cystic ducts which

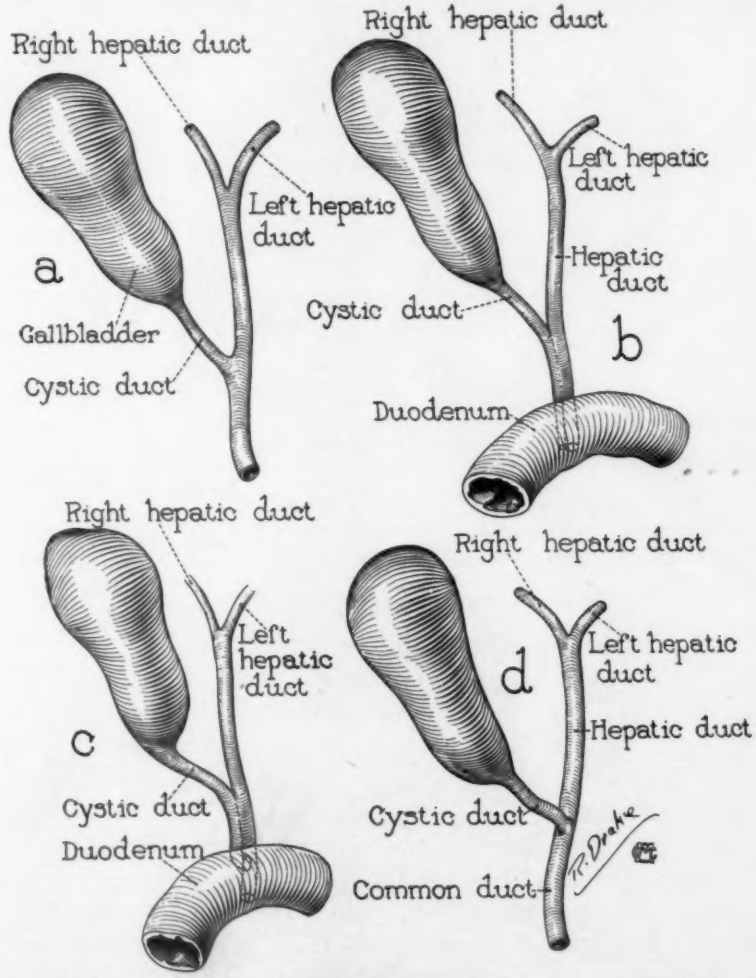

Fig. 1.—Mode of union of cystic and hepatic ducts: *a*, normal angular; *b*, long parallel; *c*, short parallel, and *d*, anterior spiral.

follow the hepatic bile duct as far as the upper border of the duodenum, as the short parallel type (fig. 1 *c*), and I have designated the ducts which extend farther, to within 1 cm. of the ampulla of Vater, as the long parallel type (fig. 1 *b*). In both of these types, however, the cystic and the hepatic ducts are bound together so intimately by fibrous connective tissue that it is almost impossible to separate them. In this

series, 26.3 per cent of the ducts were of the short parallel type and 7 per cent were of the long parallel type. The delayed juncture of the cystic and hepatic ducts, as in these variations, results in a greatly lengthened cystic duct and a relatively short common bile duct. In these aberrant cystic ducts, however, the valves were restricted to the

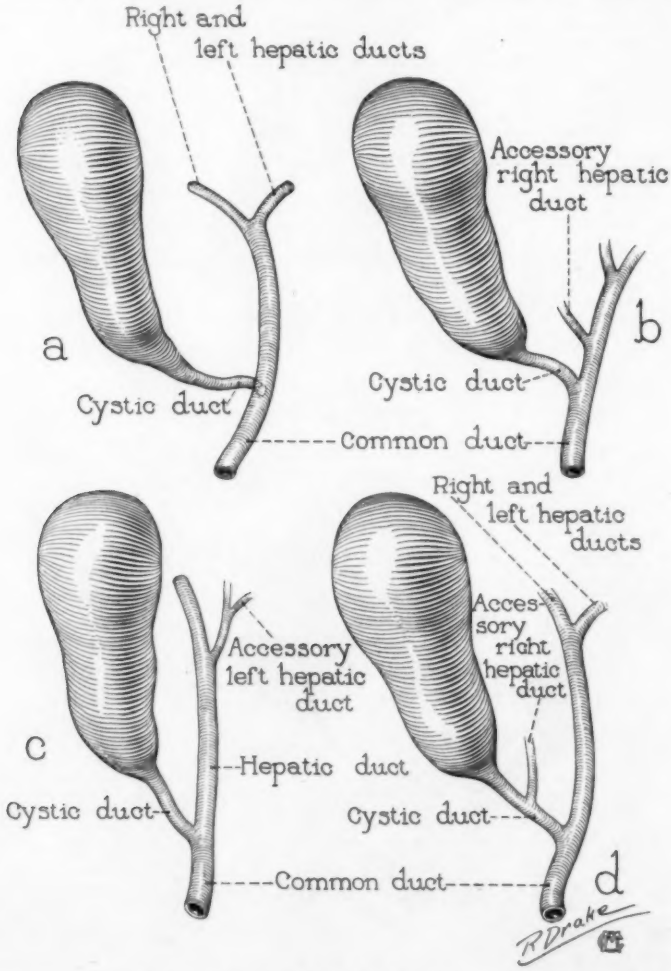

Fig. 2.—*a*, posterior, spiral mode of union of cystic and hepatic ducts; *b*, accessory right hepatic duct; *c*, accessory left hepatic duct, and *d*, accessory right hepatic duct emptying into the cystic duct.

normal site, for the remaining portion parallel to the hepatic duct was invariably patent throughout.

Of all the cases that came under my observation, 12.3 per cent could be placed in Ruge's third group, the group which includes the anterior and the posterior cystic ducts. In these variations the cystic

duct passes either anteriorly or posteriorly around the hepatic duct, describing from a quarter to a full turn around it. In my series, 7 per cent of the cases were of this anterior spiral variation (fig. 1 *d*) and 5.3 per cent were of the posterior spiral type (fig. 2 *a*).

To these three main types of anomalies, I have added a fourth, which includes variations in the distribution of accessory ducts. The first of these is an accessory hepatic duct which courses from the liver at the extreme right of the portal fissure and empties into the extrahepatic biliary tract anywhere between the point of confluence of the right and left hepatic ducts and the orifice of the cystic duct (fig. 2 *b*). This particular type of accessory hepatic duct has been hitherto described, but these accessory ducts have been found in the right side of the liver only. In my series a second accessory variation was occasionally encountered (fig. 2 *c*). This duct leaves the liver at the left of the portal fissure and empties into the left hepatic duct before the latter joins the right hepatic duct to form the main hepatic bile duct. As far as I have been able to determine, this left accessory hepatic duct has never been described before. Accessory hepatic ducts, both right and left, were encountered in 3.5 per cent of all subjects examined.

Furthermore, an additional type of accessory duct was encountered in 5.3 per cent of all cases. This duct leaves the liver on the right side of the portal fissure and enters into the cystic duct, instead of into the hepatic duct, just above the confluence of the cystic duct with the hepatic duct (fig. 2 *d*).

SUMMARY AND CONCLUSIONS

1. The normal angular mode of juncture of the cystic duct with the hepatic duct, as described in textbooks of anatomy, occurred in only a little more than half of the cases (58 per cent).

2. The long and short parallel types of cystic duct occur in more than a third of the cases and, as is shown by the literature, is perhaps the most common cause of accidents in biliary surgery. In such cases, there is a marked increase in the length of the cystic duct and a corresponding decrease in that of the common bile duct. The cystic duct and the hepatic duct are so intimately bound together by fibrous tissue that they are absolutely inseparable and thus appear as a single duct; any rough manipulation may tear the thin septum which exists between them. The large portion of a cystic duct of this type which remains following cholecystectomy may dilate and form a new gallbladder, probably with recurrence of symptoms. The cystic duct does not contain valves of Heister in the portion which lies parallel to the hepatic duct. The short parallel type occurred in 26.3 per cent of the cases in this series and the long parallel type in 7 per cent.

3. The anterior and posterior spiral varieties comprised 12 per cent of this series. The length in the anterior spiral variety conforms closely to the normal; in the posterior spiral variety the cystic duct is markedly lengthened, and the hepatic and common ducts remain about normal. It has been recorded that strong traction on the gallbladder is much more likely to tear off a spiral cystic duct than a duct with a normal arrangement.

4. Accessory hepatic ducts occurred in five cases, or 8.7 per cent of this series. Four of these were accessory right hepatic ducts, three of which were also accessory to the cystic duct. In one case there was an accessory left hepatic duct. The length and diameter of the accessory ducts corresponded closely to the normal cystic duct.

A REVIEW OF UROLOGIC SURGERY*

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KIDNEY

Surgical Technic.—Deming [1] reported a study to determine the freedom of incisions about the pelvis and the relative significance of the adjacent vessels which might be cut or ligated accidentally or purposely. He observed that following elongation of the pyelotomy incision straight on to the kidney and to the lower pole the renal circulation is not impaired if the retropelvic vessels are conserved. Angulated incisions cause definite shrinkage of the kidney. The incision of choice is the elongated incision to the lower pole near the median line. The suture of the wound in the kidney should not include any of the larger vessels. Ligation of the retropelvic vessels causes considerable renal injury which is not easily repaired in a few months' time.

Tumors.—Martin [2] stated that tumors of the kidney fall into three groups, the chief of which consists of growths arising in the renal epithelium. Tumors of connective tissue origin are represented by sarcoma, and the third group is that of the mixed tumor.

Epithelial tumors may originate from three types of epithelium. From the epithelium of the renal tubules, adenomas and carcinomas arise. Papillomas and papillary tumors spring from the epithelium lining the pelvis and calices. The hypernephroma, or third type, arises from suprarenal rests included in the kidney during development.

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* Submitted for publication, May 10, 1929.

1. Deming, C. L.: Renal Circulation Following Various Types of Elongations of Pyelotomy Incisions, J. Urol. **20**:713, 1928.

2. Martin, E. K.: Tumors of the Kidney, Brit. J. Surg. **16**, suppl. no. 13: 297, 1928.

Small adenomas not infrequently occur in the cortex of sclerotic kidneys. A single adenoma may arise in an otherwise normal kidney and grow so as to form a clinically recognizable tumor. Adenoma of the kidney, although originally benign, may become malignant.

Carcinoma of the substance of the kidney is more common in men than in women and is not especially associated with the presence of calculus. Grossly, the tumor may appear as a solid, white, infiltrating growth, which destroys and replaces the kidney without appreciably altering either its size or shape. Microscopically, this tumor is frequently a tubular adenocarcinoma, which reproduces the appearance of renal tubules.

The most common form of malignant disease of the kidney is a lobulated and encapsulated adenoma which is yellow or orange and which is often broken up by areas of necrosis and hemorrhage, as well as by the fibrous intersections between its lobules. Microscopically, a hypernephroma is composed of columns of large polyhedral cells, separated from one another by delicate connective tissue carrying thin-walled capillaries. The cells have a clear protoplasm containing fat. Parts of the tumor frequently show a compressed papillary arrangement of the cells in the columns. An exact line of demarcation between the hypernephroma and the papillary carcinoma has not been drawn.

Mixed tumors present a characteristic picture. They occur within the first three years of life, grow rapidly to a large size, and are uniformly fatal. In the early stage they are solid, opaque white, and clearly separated from the substance of the kidney. As they increase in size they may become cystic, and areas of necrosis and hemorrhage may develop. The microscopic structure is that of spindle cells in which are embedded imperfect tubules of columnar epithelium. Tracts of smooth or striated muscle are common, and other mesoblastic tissues, such as cartilage and elastic tissue, are sometimes represented.

Papilloma is a simple tumor with a marked tendency to recur and to take on malignant characteristics. Obstruction of the ureter by these tumors may cause hydronephrosis. Microscopically and grossly, the papillary character of the growth is confined to the surface. In the deeper part of the malignant tumors which infiltrate the kidney, the carcinoma is diffuse.

Sarcoma rarely occurs in the kidney in adult life.

A case of cystic adenoma of the kidney is reported. A large part of the kidney was occupied by an almost spherical tumor, which was composed of brownish material and which had been broken up by hemorrhage and necrosis. The growth was confined within a fibrous capsule and microscopically was an adenoma.

In a second case of adenoma of the kidney, the gross structure markedly resembled a polycystic kidney. The upper half of the kidney

was apparently normal. The renal capsule enclosed the growth, which was sharply demarcated from the substance of the kidney. The tumor was composed of cysts of various sizes, the largest being about 6 cm. in diameter, and the smallest almost microscopic in size.

Another interesting case is that of a papillary carcinoma occurring in one of the calices in a hydronephrotic kidney. The pelvis and calices were distended, and the renal tissue was greatly reduced. The growth occupied one of the lower calices, had infiltrated the surrounding substance of the kidney, and was visible on the surface of the organ. Microscopic examination disclosed squamous cell carcinoma.

Deming [3] reported a case of sarcoma of the kidney in a boy, aged 29 days. Nephrectomy was performed under local anesthesia. The tumor was so large that approach was made through an incision in the right rectus muscle extending from the costal margin to the pelvis. The muscles were separated and the peritoneum was opened, exposing the tumor which extended from the liver above, being overlapped by it, to the pelvis below and to the umbilicus mesially. It was adherent above to the liver and the gallbladder, mesially to the ascending colon, and at its lower pole to the cecum and appendix. The adhesions were carefully freed, and the tumor was mobilized. But, as it was otherwise impossible to demonstrate the pedicle, the cyst was tapped, and about 100 cc. of blood and gelatinous fluid was aspirated. The pedicle was then clamped and ligated. The wound was closed in layers, with a small rubber tissue drain inserted at the lower angle. The patient withstood the procedure well, manifesting shock only when the pedicle was being held tense. He recovered readily from the operation and was well six and a half years later. Pathologic diagnosis was congenital spindle cell sarcoma of the kidney.

[COMPILER'S NOTE: The rarity of complete cure of sarcoma of the kidney in a young child makes this case of interest. The majority of cases of tumors of the kidney occurs in the first two years of life. Rarely is one seen and the patient operated on at such an early stage as that reported by Deming. Tumors are generally confined by the renal capsule. They may occur in any part of the kidney and generally involve the entire organ. Metastasis is uncommon and when it does occur is generally in the late stages. If metastasis or local extension has occurred, operation is often followed by a rapidly fatal outcome. Nephrectomy in most cases prolongs life and offers the patient the only chance of improvement. Earlier writers agree on the high mortality. Newer methods of surgical approach, improved asepsis, and at times avoidance of the peritoneal cavity have in most instances greatly

3. Deming, C. L.: Sarcoma of Kidney; Cured, New England J. Med. **199**: 273, 1928.

reduced the older mortality figures, but definite cures, such as the one cited here, are few.]

Beer [4] found it necessary to perform nephrectomy in 18 per cent of 271 cases of stone in the kidney in which renal tissue was destroyed. Pyelotomy, with or without nephrotomy, was the procedure of choice in the remainder of the cases. In 29 of the last 38 cases, he performed pyelolithotomy and in 1, wide nephrolithotomy. The increased use of pyelolithotomy was due to the fact that it saves the parenchyma of the kidney and assures complete removal of all calculous material. It may also be used in cases of complicated stones.

If the kidney cannot be delivered and it is necessary to perform nephrotomy, Beer performed a bloodless operation by placing a rubber tourniquet around the pedicle. In all cases he followed the principles of constricting the ureter to prevent fragments from falling into it and of having the roentgenograms of the kidney developed immediately after removal of the stones. In about fifteen cases of stones of complicated shape, fragments were still present but were easily located and removed.

Randall [5] stated that there are three prevailing theories regarding the etiology of formation of stone. The first is the action of specific bacteria. The second is based on colloidal chemistry, beginning with the facts that calculi result from an abnormal type of crystalline precipitation, that normal urine holds water-insoluble crystalloids in solution because of the presence of protective colloids, that hydrogen ion concentration affects this solution, and that the colloidal matter in solution modifies the morphology of crystalline precipitates. Basing his experiment on these factors, Keyser produced calculi by disturbing the urinary colloidal balance. He concluded that this disturbance may be due to quantitative changes in the colloids normally present, or to the entrance of abnormal colloids into the urine, either from the blood stream or as products of local renal disease. The frequency of formation of stones in animals having a diet deficient in vitamin A is the basis for the third theory. Such calculi consist essentially of the characteristic insoluble phosphates of calcium and magnesium, and treatment by dietary measures has resulted in the successful disappearance of these stones.

In from 3 to 81 per cent of the cases, the nucleus of stones was composed of urates and uric acid. Oxalates were present in ratios from 5 to 66 per cent.

Randall expressed the belief that vesical calculi are uniformly secondary formations to foreign bodies, to vesical obstructions causing

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4. Beer, Edwin: Bermerkungen über die Tecknic der operativen Entfernung von Nierensteinen, Ztschr. f. urol. Chir. **24**:601, 1928.

5. Randall, Alexander: Rapidity of Growth of Urinary Calculi, Atlantic M. J. **31**:937, 1928.

residual urine, to vesical diverticula, to renal lesions and to descending stones. Incomplete prostatic operation which prevents complete emptying of the bladder often predisposes to secondary formation of stones. It is recognized that phosphatic stones grow more rapidly than others and that their growth is markedly influenced by the presence of a foreign body or alkaline cystitis.

Randall reported the growth of a stone in one of his patients who had taken some pills containing methylene blue (methylthionine chloride, U. S. P.) for urinary trouble. At operation three years later, two calculi measuring 3 by 2.5 by 1.5 cm. were removed. On section, each appeared to be formed of pure ammonium urate; the laminae in the early growths were stained green, showing a growth of 2 cm. in the three year interval. In another of Randall's cases three stones were removed from the bladder, the largest measuring 4 by 3 by 2 cm. The growth, in eighteen months, was due to alkaline cystitis and a contracted vesical orifice. In a museum is displayed a string of four calculi, the largest measuring 3 by 3 by 2 cm., all adherent to a linen thread, which probably had been misapplied during herniotomy five months before.

Nay [6] stated that renal stones should be considered recurrent only when proved not to have been overlooked. He expressed the belief that infection is the cause of calculi in a large number of cases. Preoperative treatment should consist of removal of the focal infection, if possible, and treatment of the kidney. Postoperative treatment is important because it helps to reduce the recurrence of stones by leaving the patient with a good uninfected kidney.

Herbst, in discussing the recurrence of stone in the kidney, considered that focal infections play only a small part in the cause and recurrence of lithiasis. It is his belief that renal retention and infection are the important factors in the production and reappearance of renal calculi, and that the correction of these conditions following removal will reduce the number of recurrences.

Mattes [7] stated that urolithiasis is considered of rare occurrence in the colored race. In 1913, Pfister reviewed the literature and noted particularly the occurrence of renal stone in the colored people of Africa, South America and the German colonies. He observed that the appearance of calculi depends on the locality, the soil and the water, and that in some regions it is almost unknown. Pfister stated the belief that if the examination of the two races was equally thorough, stone would be found as frequently in the colored as in the white race. Mattes' figures show that there was three colored persons with stone to seven white in 1924, and in 1925 he noted a ratio of one colored to five white persons.

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6. Nay, E. O.: Prevention of Recurrent Renal Calculi, J. Urol. **20**:553, 1928.

7. Mattes, A.: Renal Calculi in the Colored, South. M. J. **20**:941, 1927; abstr., Ztschr. f. urol. Chir. **24**:408, 1928.

Walthers stated that formation of stone in the negro was rare and that he had seen few cases. During a period of ten to twelve years in a hospital for the colored, Righton never observed stones although many roentgen examinations were made. Hayes did not observe a single case in three years. Many other urologists, among them Kelly, who sees a great many negro patients, report similar experiences.

Ray [8] stated that urinary calculi commonly consist of certain substances insoluble in water and urine. Crystals of these substances are sometimes found in normal urine, but they are generally isolated and single. These particles may be held in solution, may deposit a fine sediment, or may form calculi, and are brought about by colloidal substance. Ray believed that the absence of colloids in the urine is brought about by certain pathologic conditions within the kidney, due either to local disease or to outside influences reacting on the organ.

Billington [9] attempted to assess the value of the results of nephropexy. He considered it from two aspects: (1) the surgical success of the operation permanently replacing the kidneys in their normal position without unsatisfactory sequelae, such as pain in the loin or back, hernia of the wound and persistent sinus, and (2) its therapeutic value in curing or ameliorating the symptoms for which it is performed. At first the results were not satisfactory. In a large percentage of cases the operation failed to cure the abnormal mobility of the kidneys, and they were found loose again as soon as active life was resumed. Many operations fixed the kidney to the muscles of the back at too low a level, with the result that pain in the back was common and at times hydronephrosis developed. The use of silk and other nonabsorbable suture materials was followed by persistent sinuses, and extensive injury to the muscles of the loin led to a feeling of weakness and hernia. A further and common cause of failure is the incomplete character of the operation. One kidney only is replaced, while the other one, which may also be mobile, and a possibly diseased appendix are left untreated. Only when the surgeon is satisfied that both kidneys are in a normal position and that associated or secondary abdominal lesions may have been excluded or treated can success be claimed.

Billington has performed nephropexy on 1,500 patients, and it has been his object to replace both kidneys, if necessary, and to make sure that intra-abdominal lesions were not left undetected and untreated. The surgical results were satisfactory; in not a single instance has he found a kidney loose again. Of 163 patients who were traced, 71 (43.6 per cent) reported that the operation was successful, 41 (25 per cent)

8. Ray, D. P.: Etiology of Urinary Calculi, Atlantic M. J. **31**:934, 1928.

9. Billington, William: The Therapeutic Value of Nephropexy, Brit. M. J. **2**:975, 1928.

reported that it was partially successful, usually indicating relief of renal symptoms but not all associated symptoms, and 51 (31.4 per cent) reported failure.

Pyelonephritis.—LeComte [10] discussed the anatomic changes brought about by pregnancy and their influence on renal drainage. It is a well-established principle of urinary lesions that any obstruction will sooner or later cause infection; its duration will depend on the degree of obstruction, and the extent of injury will depend on the length of time it is permitted to act. A second principle is that the hazard to the integrity of the kidney is in proportion to the distance that the obstruction occurs from it. Frequent painful urination and pyuria should be considered as indications of a possible serious infection of the kidney.

During pregnancy, the form of the urinary organs is changed and function is disturbed by the enlarging uterus. The urethra is elongated early and the bladder is soon compressed and drawn upward, so that by the third month it becomes an abdominal organ. Functionally, these changes lead to frequency and residual urine, with the common sequence of bacteriuria and inflammation. Sluggish peristalsis was noted in 80 of 100 normal pregnant women on whom cytoscopy was performed. The abdominal ureter and renal pelvis are commonly found dilated during pregnancy. Varying degrees of dilatation were noted in all normal pregnant and parturient women who were submitted to pyelography; all presented symptoms of renal pain, or infection was present. While changes are taking place in the lower tract, the ureters and renal pelves are being slowly dilated by the intermittent obstruction afforded by the enlarged uterus. In some cases, due to the patient's high resistance or the absence of bacteria specific for the tissues at hand, the process stops; in others, inflammation results. Occasionally a vicious circle is established, the bladder becoming infected and the kidneys becoming reinfected from the bladder, this infection occurring either from the blood stream or ascending along the lymphatics of the ureter. If these changes occur early in pregnancy and are not relieved by treatment, the fetus usually dies from the infectious toxemia and the uterus empties spontaneously.

LeComte stated the belief that the greatest aid in the recovery of an infected kidney is the establishment of free drainage. During pregnancy, this may be brought about independent of whatever treatment is given and may lead to a good result. In the way of treatment, rest in bed during the febrile intervals is indicated, and the patient should lie on the side opposite that infected as much as possible, in order to relieve the pressure of the uterus on the ureter by gravity.

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10. LeComte, R. M.: Kidney Infections During Pregnancy, Virginia M. Monthly **55**:481, 1928.

Duncan and Seng [11] reported a survey of the protective mechanism of the urinary tract of healthy pregnant and puerperal women. They observed that physiologic forces external to the ureter cause obstruction to ureteral and renal drainage in pregnancy, which is relieved almost immediately on termination of gestation. Right-sided ureteral dilatation is constantly present; hydronephrosis on the right occurs only slightly less frequently. The left ureter and renal pelvis escape this dilatation in a high percentage of cases. Bilateral hydro-ureter and hydronephrosis were of common occurrence, and were apparent earlier, more frequently and in more marked degree in the multipara than in the primipara.

Stasis, as measured by inability of the renal pelvis and ureters to empty themselves within the normal time limits, is definitely and almost universally observed in women before delivery. It is still persistent in a less degree over a prolonged period after delivery.

Duncan and Seng demonstrated an unexpected amount of pus and coliform organisms in specimens from the bladder and kidney of supposedly healthy pregnant women and in women after delivery. They concluded that every pregnant woman has some degree of obstruction, definite dilatation of the ureters and renal pelves, and well defined stasis continuing over a long period. They further demonstrated that in the apparently healthy pregnant and puerperal patients there is a probable renal complication, the presence of pus and coliform organisms. The line of demarcation between the physiologic and pathologic conditions in these cases is fine. These authors expressed the belief that these women are all subjects for potential pyelitis.

Blanton [12] stated that pyelitis is the most common urologic disturbance found during early life. It may arise as a primary infection but usually follows some other acute infection, such as tonsillitis, bronchitis or pneumonia. As a primary disease it is usually present during the early months of life, and mainly in girls, as a result of the proximity of the urethral opening and the anus and also of the short urethra in the female. It is caused chiefly by the colon bacillus and tends to be an ascending infection, the bacilli traveling up through the urethra and bladder to the pelvis of the kidney by way of the ureter or lymphatics. It may also be due to direct extension of infection from some nearby organ, such as the appendix or other portion of the intestinal tract. When it results from a hematogenous infection, the causative organisms are carried from some distant focus to the reinal pelvis, where inflammation occurs. Any obstruction to the urinary flow from the kidney

11. Duncan, J. W., and Seng, M. I.: Factors Predisposing to Pyelitis in Pregnancy, Am. J. Obst. & Gynec. **16**:557, 1928.

12. Blanton, J. L.: Pyelitis of Infancy and Childhood, Virginia M. Monthly **55**:479, 1928.

predisposes to infection. The common causative organisms, in their order of frequency, are the colon bacillus, *Staphylococcus albus* and *Staphylococcus aureus*, the streptococcus, the typhoid bacillus, the pneumococcus and *Bacillus pyocyaneus*.

The acute form of pyelitis is characterized by sudden onset, frequently with a chill, followed by high fever and sweating. Chronic pyelitis may follow the acute form, or it may arise as a complication of some other disease and pass unrecognized unless discovered by urinalysis. It may exist for months or even years without causing typical symptoms.

Alkalis or antiseptics may be used in the treatment for acute pyelitis. The alkaline treatment is indicated in those cases in which the urine is acid, small in quantity and full of pus cells. Some alkaline diuretic, such as potassium citrate or acetate, or a combination of alkaline diuretics, should be used and fluids forced. If the pyuria is not cleared up promptly by this method, Blanton uses the antiseptic treatment, which tends to make the urine sterile. The common antiseptic used is hexamethylenamine or methenamine. He considers the cytoscope an aid in the treatment of many patients, even young children. The attempt should be made to eliminate all obstruction to the urinary flow and to treat the condition locally by means of lavage with antiseptic solutions; this is often successful when medical treatment fails.

Tuberculosis.—Greifenstein and Kehl [13] reported forty-three nephrectomies for renal tuberculosis performed at the surgical clinic of the University of Marburg between 1891 and 1923. A follow-up study was possible in forty-one cases. The period of operative mortality extended from one to six months. In a second danger period of from one to three years, deaths caused by tuberculous complication occurred. Thirteen patients died. This high mortality was due to the primitive diagnoses and treatment of the earlier period. Histologic studies frequently disclosed bilateral renal tuberculosis when clinical proof was lacking. The mode of infection of the second kidney was the same as that of the first, namely, hematogenous. Infection by the urinary route can occur only in cases of advanced tuberculosis of the bladder.

The follow-up study of cases in which nephrectomy was done revealed that the patients remained tuberculous and succumbed sooner or later to tuberculosis. The prognosis appears more favorable in women. In men, genital tuberculosis does not exert any greater influence on the prognosis than that of any other organ, provided it is not complicated by active pulmonary tuberculosis. Of thirteen patients

13. Greifenstein, A., and Kehl, H.: Die Ergebnisse der Behandlung der Nierentuberkulose in der chirurgischen Klinik zu Marburg, Deutsche Ztschr. f. Chir. **208**:1, 1928.

living, eight were entirely cured, four were improved, and one was worse. Injury to the peritoneum during nephrectomy on the right side rarely resulted in peritonitis. On the other hand, infection of the wound and the formation of fistula occurred in 17 per cent of the cases. The method of treating the stump of the ureter did not seem to be of any significance in this connection. The fistulas healed, as a rule. Nonsurgical treatment of renal tuberculosis is not to be considered, although in rare cases cure is possible through complete destruction of the organ in the absence of all symptoms.

Scholefield [14] reported seventy-four cases of renal tuberculosis with fifty-nine nephrectomies from the Peter Bent Brigham Hospital. Two patients died within the first few weeks after the operation, and six died after a few years. Eighteen of the patients traced are known to be alive and well more than three years after the operation, while only eight are known to have continued symptoms of urinary tuberculosis. The remaining twenty-five were observed recently, or were lost track of before the end of three years.

Of the fifty-seven patients leaving the hospital, twenty-three (40 per cent) reported primary healing of the lesions, which remained healed. In twenty-four cases (42 per cent) sinuses developed which required attention for from three months to several years.

Scholefield concluded that in cases in which, at operation, the kidneys appeared little diseased sinuses were more apt to occur than in those in which extensive caseation was present. Involvement of the ureter or of the perinephric fat did not seem to have any bearing on the healing of the wound. The average period during which symptoms had been present was twenty-eight and six-tenths months in cases in which lesions healed, and sixteen and three-tenths months in those in which sinuses developed. The more acute the process, therefore, the more likelihood there is for the development of a sinus. Scholefield suggested that these sinuses are due not to the continuation of any existing infection but to the development of a new tuberculous process in the traumatized tissues of a patient whose resistance is lowered.

Cathelin [15] stated that the dictum of Albarran that early nephrectomy is essential in renal tuberculosis still holds good. He discussed several complications following the removal of tuberculous kidneys.

Lumbar fistula is a commonly observed sequel after renal tuberculosis. Twenty or thirty years ago, fistulas were common, but today, with the present methods of surgical technic, they are fewer. So-called

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14. Scholefield, B. G.: Renal Tuberculosis: Healing of Tuberculous Nephrectomy Wounds, J. Urol. **20**:345, 1928.

15. Cathelin, F.: Les séquelles de néphrectomie pour tuberculose rénale, Rev. gén. de clin. et de thérap. **42**:321, 1928.

urétéraux forcés, or dilated ureteral orifices, with urinary reflux, are rare at the present time.

Cathelin reviewed the histories in forty-five cases of nephrectomy. In most of them the lesions healed in from five to ten months, and in the majority of the remainder, in from ten to sixteen months after operation. In three of the cases the condition lasted for from eighteen to twenty-two months; in one for twenty-four months, and in another for thirty-one months. Cathelin follows two primary rules: he never washes the wound, and touches the base of the wound as little as possible. Reopening of the wound occurred in fifty of Cathelin's cases.

Occasionally there is considerable pain in the remaining kidney, due usually to hypersecretion and hyperfunction. This painful phenomenon is usually explained by simple reflex excitations and intermittent congestion.

Continuation of the symptoms in the bladder occurs in about 50 per cent of the cases. In half of these there is no change following operation, and in the other half there is moderate amelioration. In the remaining 50 per cent of the cases, the condition clears up completely. Cathelin uses oil of gomenol, 10 per cent strength, injecting 5 cc. every second day. On alternate days days bladder lavage is carried out.

Fronstein [16] stated that 80 per cent of patients with renal tuberculosis who are treated by conservative methods die in the course of five years after the onset of the disease. After ten years, practically none is living. On the other hand, about 75 per cent of patients operated on live their normal span of life. The postoperative results vary directly with the length of time the symptoms have been present preoperatively. The earlier the diagnosis and operation, the more satisfactory the results. One of the significant diagnostic points is the finding of bacilli of tuberculosis in the urine. Albuminuria is also of significance. Fedoroff observed albuminuria in 85 per cent of his cases. In Fronstein's series, it occurred in all cases. Dysuria is an early symptom and occurs in 94 per cent of the cases. Pyelography is of exceptional value in diagnosis.

Fain [17] stated that while the bacillus of tuberculosis causes specific changes, it may at the same time bring about nonspecific nephritis, nephrosis and cirrhotic changes. In such a tuberculous kidney, tubercle formation is frequently not to be discovered. The course of a nonspecific renal change may be slow and end with contraction. With nonspecific tuberculous nephritis there may also be specific changes, and for that reason the diagnosis may be undetermined in each case. The pathologic-anatomic mutations show the frequency of bilateral tuber-

16. Fronstein, R.: Le diagnostic de la tuberculose rénale, J. d'urol. **25**:434, 1928.

17. Fain, L.: Ueber die Frühdiagnose und Therapie der Initial formen der Tuberkulose der Harnorgane, Ztschr. f. urol. Chir. **24**:421, 1928.

culous nephritis. Clinically, the differential diagnosis of tuberculous nephritis and tuberculous bacilluria is quite difficult and sometimes impossible, especially if there is a history of a common disease of the kidney. The difficulty in diagnosis is due to the similarity of the clinical manifestations of these diseases, which necessitate long observation and repeated examinations of the patient. In nonspecific renal changes associated with a tuberculous bacilluria or tuberculous nephritis, the absence of pyuria or the presence of slight or easily treated pyuria of the pelvis is characteristic; at the same time, the cystitis is of the nonulcerative type and treatment is carried out in the usual manner, with relief. The additional renal pyuria which does not yield to the customary treatment, associated with severe cystitis and diminution in renal function, shows in most cases a destructive renal tuberculous infection. In the event of operative treatment for nonspecific infections of the kidneys which permit the passage of bacilli of tuberculosis, or in kidneys showing tuberculous nephritis, it is advisable to use some conservative procedures, such as decapsulation, nephrotomy, pyelotomy or ureterotomy. Such patients must remain under constant observation, since the kidney operated on conservatively is in continual danger of undergoing tuberculous changes and necrosis.

Cystic Disease.—Crosbie [18] stated that large solitary cysts of the kidney should not be confused with smaller cysts occurring in nephritis and in sclerotic kidneys. Large cysts are usually unilateral and never connect with the renal pelvis, and the remaining renal tissue is as a rule normal. The cyst is usually situated at one pole of the kidney. It is more common in woman than in man, and the fluid is clear, straw-colored and rarely bloody. Symptoms are referable to the pressure of the cyst either on the remaining part of the kidney or on other organs. Hematuria is rare.

Treatment is operative. If the cyst is situated at one pole, it may be possible to do a resection and save the remainder of the kidney. Crosbie reported the case of a large cyst in the median portion of the kidney, in which nephrectomy was performed. On section the cyst was found to be lined by smooth, shiny, glistening tissue. There was an incomplete septum which partially lobulated the cyst. The fluid content was pale and clear, and there was no evidence of infection.

Barney, in discussing Crosbie's paper, reported a case of renal cyst in which the main symptoms were hematuria and retention of urine. At operation the kidney seemed to be in good condition elsewhere, so he trimmed off the cyst at its juncture with the cortex. In an effort to

18. Crosbie, A. H.: Solitary Cyst of the Kidney, New England J. Med. **199**: 277, 1928.

dissect out the lining membrane of the cyst from the cortex, he encountered considerable bleeding, so instead the cavity was swabbed out with Zenker's fluid.

Blood Supply.—Ferrer [19] stated that distention of the renal pelvis and calices to their normal capacity will produce distinct, partial obstruction to the outflow of venous blood in the kidney, which is proportionate to the degree of distention. Any obstruction to the free outflow from the renal pelvis will tend to produce renal passive congestion, and a continuously distended pelvis may aid in the formation of hydronephrosis.

Ferrer expressed the belief that pyelovenous backflow is only a temporary phenomenon, and will persist only as long as the venous outflow fails to increase in pressure sufficiently to overpower that of the backflow. A more complete understanding of this type of obstruction will lead to better use of a permanent catheter, or at least of ureteral drainage and dilatation in many of the obstructive uropathic conditions encountered, especially in pregnancy. Pyelography should be done with care, and there should be a tendency to rely more on small amounts of concentrated solution than on weak but larger amounts of fluid.

Renal Reflexes.—Papin [20] stated that the nerve tracts of the kidney and its pelves carry two types of fibers, sensory and vasomotor, and that there are two types of reflexes, plain and secretory. Only the normal kidney is the seat of pain sensations. One of Papin's cases is illustrative of this. There was severe pain in the left loin due to right-sided hydronephrosis. Following removal of this lesion, the pain in the left kidney disappeared. Up to the present, observations show that the reflex pain in the normal kidney more often is associated with nephrolithiasis and less frequently with movable kidney, hydronephrosis, pyelitis, tuberculosis and renal tumors.

In the involvement of the kidney, and especially of the renal pelvis, the pain is not precipitated in the organ itself, but is referred to the corresponding Head's area on the surface of the body, usually on the same side; occasionally it is referred to both sides and in rare cases to the opposite side.

The problem of reflex secretory disturbances is still far from being clearly understood. Its manifestations are oliguria and, in rare cases, polyuria. Clinical observation has shown the following types: fatal anuria in unilateral obstruction; oliguria in a unilateral lesion, which

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19. Ferrer, J. C.: Obstruction to the Venous Circulation in the Kidney Caused by Distention of the Pelvis and Calices, with Special Reference to Pyelovenous Backflow, J. Urol. **20**:701, 1928.

20. Papin, E.: Actions réflexes réno-rénales, Arch. d. mal. d. reins **2**:518, 1927; abstr., Ztschr. f. urol. Chir. **24**:335, 1928.

may be aided by removal of the diseased kidney; transient anuria following nephrectomy or a conservative renal operation, and polyuria after nephrectomy. One form of reflex polyuria occurs in tuberculosis, explained by Graser as a reflex of the pathologic conditions of the kidney brought about by vesical pollakiuria. Papin observed true reflex polyuria of the normal kidney in a case in which nephrectomy was done for hydronephrosis associated with infection. Clamps were left in place because of a short pedicle; polyuria developed, the amount of urine reaching 6,000 cc. by the fifth day. Following removal after the clamps were removed, the output diminished to 2,000 cc., where it remained.

Experimentation has not furnished any definite facts. The production of reflex anuria has been successful only in rare cases in which the condition was not clearly defined. The question as to whether anuria can occur in a normal kidney, whether the anuria may be permanent, or whether it disappears with the removal of the cause has not been solved. According to Neuwirth, reflex anuria is brought about through a spastic condition of the intrarenal vessels, which come through the vasomotor paths. This reflex is abolished by a break in the vasomotors (splanchnic anesthesia). Further researches of Neuwirth, and later of Koennekes, have shown that the splanchnic nerves carry not only vasomotor but sensory fibers, afferent and efferent, which can be affected by the same factors.

The question of reflex polyuria is even more doubtful. Experimentally, the only fact proved is that there is a polyuria center in the tuber cinereum of the medulla. Polyuria caused by splanchnic section is only transient, and always involves the same side.

Papin noted that clinical experience has yielded a few facts to explain some of these secretory disturbances. Nephrectomy has usually been difficult, and either the clamps were left on the pedicle or the ligatures had to be applied close to the large vessels. This probably caused direct irritation or destruction of the ganglions in these coursing reflex tracts.

Wounds.—Harris [21] reported a case of rupture of the kidney which he diagnosed by means of pyelography more than three weeks after the injury. He was impressed by the tremendous recuperative and reparative power of the kidney. He stated the belief that these patients are generally not observed long enough to determine that mechanical defects have not, at a later date, been followed by complicating infection and even by the formation of stone, resulting ultimately in destruction of renal tissue. He drew the following conclusions: ureteropyelographic study should be done in every case of renal trauma, after all acute

21. Harris, A.: Traumatic Rupture of Left Kidney: Case Report, J. Urol. **20**:193, 1928.

symptoms have subsided. The time to investigate depends on the symptoms in the individual case and the judgment of the surgeon. More complete follow-up study should be carried out over a long period in every case to control secondary complication of infection and the formation of stone as far as possible. Chronic infection without obstruction might continue for long periods without symptoms sufficient to necessitate the consulting of a physician by the patient. Catheterization and renal lavage might be valuable in controlling infection. The reparative power of the kidney is remarkable. Open operation is indicated only in the exceptional, extreme case of renal injury, with uncontrollable hemorrhage. Infection following extravasation of urine or hematoma may require drainage. It is possible that an infected pouch, sinus or sac, not relieved by lavage, might be removed by open operation, the kidney being conserved at the same time. An accessory pouch seen in the pyelogram must be distinguished from solitary cyst of the kidney.

Suprarenal-Renal Heterotopia.—Caylor [22] considered suprarenal-renal heterotopia as an anomaly of surgical and general significance, and defined it as the developmental inclusion of the suprarenal gland beneath the capsule of the kidney. Rests of suprarenal tissue are not included in this group, as they are usually made up of cortical cells, in contrast to true heterotopia in which both cortical and medullary elements are present. All or only a part of the suprarenal gland may be beneath the renal capsule.

Caylor found thirteen cases reported in the literature, and he added a fourteenth. A well developed woman, aged 34, apparently in good health, came to the Mayo Clinic for general examination. In the course of the examination, hydronephrosis of the right kidney was discovered. This kidney had a low functional value, while the left kidney functioned normally. The right kidney was removed through a lumbar incision. An accessory vessel to the right kidney was thought to have been a factor in causing the hydronephrosis. The kidney weighed 180 Gm. The hydronephrotic dilatation of the pelvis had apparently destroyed from 30 to 40 per cent of the parenchyma, and the anterior-superior surface of the kidney was partially covered with a yellow plaque, the suprarenal gland. As the capsule was stripped from the kidney, the gland was found intact beneath it, instead of in its usual situation in the perirenal fat. Duplication of the gland was not found.

Postoperative Statistics.—Hunt [23] reviewed the major surgical conditions arising in the kidney in cases observed at the Mayo Clinic during

22. Caylor, H. D.: Suprarenal-Renal Heterotopia: Report of a Case, J. Urol. **20**:197, 1928.

23. Hunt, V. C.: A Review of the Surgery of the Kidney, Proc. Staff. Meet. Mayo Clinic **3**:201, 1928.

the last six years. During this period, 1,640 operations were performed on the kidney. Nephrectomy was performed in 1,119 cases (68 per cent). In 157 of the cases, the disease was malignant; 11 patients died following nephrectomy, a mortality of 7 per cent. The remaining 962 nephrectomies were performed for benign disease, with 20 deaths, a mortality rate of 2 per cent. Five hundred and twenty-one conservative operations were performed on the kidney largely for lithiasis, with 8 deaths, a mortality of 1.5 per cent.

Renal stone was the most common surgical lesion, comprising 808 cases (49.2 per cent). Nephrectomy was performed in 287 (35.5 per cent) of the total number of cases of lithiasis. Seven deaths (2.4 per cent) occurred, as opposed to 1.5 per cent for the conservative operation. There were 521 conservative operations, such as pelviolithotomy (85 per cent), nephrolithotomy, or the combined operation.

Nephrectomy was done for renal tuberculosis in 305 cases (27.2 per cent). There were 6 deaths, a mortality of 1.9 per cent. In 336 cases (30 per cent of all the conditions that required nephrectomy) the operation was performed for pyonephrosis, pyelonephritis and hydronephrosis with infection.

One hundred and fifty-seven nephrectomies were performed for malignant disease of the kidney. Hypernephroma was the predominating lesion, occurring in 113 cases (72 per cent of all the malignant lesions); carcinoma, 20 cases (12.7 per cent); epithelioma, 17 cases (10.8 per cent), and sarcoma, 7 cases (4.4 per cent).

Operation was performed in 23 cases of fused or horseshoe kidney. There were 12 cases of renal lithiasis in which the stones were removed by pelviolithotomy.

Heminephrectomy was necessary in 6 cases of hydronephrosis; cysts were drained in 2 cases, exploration for pain was carried out in 2 cases, and accessory vessels were divided in 2 cases.

Braasch, in discussing Hunt's paper, stated that more than 30,000 cystoscopies had been performed during the same period. During these six years, there were a great many more patients with surgical lesions of the kidney who were not operated on for various reasons. Fully a third of the patients came with symptoms not referable to the urinary tract; possible involvement of the kidney was suggested only after careful examination. The mortality rate in nephrectomy performed for renal tuberculosis was 1.9 per cent, which is about the same as that in the total number of cases in which operations were performed on the kidneys.

Wildbolz recently quoted statistics of a series of 640 nephrectomies, showing a mortality of 2.8 per cent. He stated, however, that this number included a series of more than 100 cases in which operation

was performed without a fatality; this is further evidence that statistics based on a small number of cases are without value.

Attention was called to the high percentage of patients with renal lithiasis in whom it was necessary to remove the kidney. Braasch stated that the general practitioner is often largely responsible for this, since if he had insisted on investigating the cause of the patient's colic and if after the diagnosis of stone had been made he had insisted on operation, a conservative operation might have been possible. A conservative operation, of course, is best because of the possibility of bilateral lithiasis, if for no other reason.

URETER

Infection.—Kidd [24] suggested that the ureter should be examined carefully before nephrectomy is done, as in selected cases the removal of the major portion of the ureter, besides the kidney, will be found to give better results. In cases of hydronephrosis, if the obstruction of the ureter is in the pelvic region and the ureter as far as the obstruction is not removed, the portion remaining frequently causes trouble. The ureteral stump may remain infected and cause attacks of colic, fever and strangury, or a large infected pouch may form. In some cases, these attacks of dysuria and fever resulting from ureteral retention are relieved by the passage of purulent urine.

Some surgeons remove as large a portion of the ureter as possible when removing a tuberculous kidney; others consider that this step entails risk of the formation of an abscess or urinary fistula deep in the pelvis. Kidd believed that in cases of septic stones impacted in the pelvic ureter with a dilated atrophic ureter above, primary nephro-ureterectomy should be done. If the lumen of the ureter is not obstructed, complications will rarely arise even if the ureter is left in place. The inflamed and infected ureter will gradually atrophy and its contents become sterile. If the process of sterilization is delayed, it can be hastened by washing out the stump of the ureter. Kidd has noted that in many cases after operation for calculous pyonephrosis the stump of the ureter has become aseptic and has not given further trouble. On the other hand, if there is an obstruction between the site of the ligature and the bladder, trouble will probably arise in the stump of the ureter; the muscular wall will hypertrophy in an endeavor to get rid of the contents of the ureter, causing attacks of ureteral colic. The lumen of the ureter may become dilated and cause severe symptoms of urinary infection.

Kidd gave the following indications for primary nephro-ureterectomy: (1) in hydronephrosis, simple or infected, when the stricture is

24. Kidd, Frank: The Stump of the Ureter After Nephrectomy: Indications for Primary Nephro-Ureterectomy, Brit. J. Surg. **16**:22, 1928.

low in the pelvic ureter; (2) in pyonephrosis or atrophic septic or aseptic kidney secondary to a stone long impacted in the pelvic ureter; (3) in tuberculous pyonephrosis associated with inflammatory stricture in the pelvic ureter, and (4) in all other types of pyonephrosis associated with inflammatory stricture in the pelvic ureter.

In most cases in which Kidd performs primary nephro-ureterectomy he cuts down on the kidney from behind, and after it has been freed and its pedicle tied, he frees the lumbar ureter from its connections, taking care to tie all bleeding points, which may be numerous. The ureter can be burned across with a cautery, or the kidney and ureter can be left hanging out of the lower margin of the wound, which is then stitched up and the patient turned on his back. In the cases in which operation is more easily performed and in which the obstruction is high in the pelvic ureter, such as a stone, the ureter is then exposed extraperitoneally through a muscle-splitting incision for exposing the pelvic ureter, tied off with catgut below the point of obstruction, burned across, and with the kidney is drawn out from the wound in the back. If a drain is carried to the stump of the pelvic ureter, it should consist of a piece of rubber glove; tubes endanger the walls of the iliac vessels and should not be employed. If, on the other hand, the operation is difficult and the obstruction lies close to or even in the walls of the bladder, a better exposure can be obtained by turning the rectus muscle outward from near the median line below the umbilicus. Through this incision the ureter can be stripped extraperitoneally to the wall of the bladder; the numerous branches of the internal iliac and other vessels running to the wall of the pelvic ureter and bladder can be exposed and tied off, and the ureter can be completely removed. In some cases it has even been found necessary to remove a portion of the wall of the bladder, a step that is feasible through this incision.

Read [25] reported a case of empyema of the ureteral stump in a woman, aged 31. One week after hysterectomy, pus appeared in the urine. Three months later, a ureterovaginal fistula was found. The end of the left ureter was located in the fibrous tissue of the pelvis and transplanted into the upper angle of the bladder. The vaginal fistula healed, but foul pyuria persisted, and pain in the lower left quadrant and lower lumbar regions became increasingly severe. Six weeks later the pyuria was more severe, and left nephrectomy was performed. Pathologic examination disclosed general pyonephrosis. Two months after the nephrectomy the patient began to have severe, shooting pains along the course of the left ureter, radiating into the bladder. The attacks came on suddenly and lasted for from two to seven days.

25. Read, J. S.: A Ureteral Stump (Non-Tuberculosis) as a Source of Pyuria: Case Report, J. Urol. **21**:103, 1929.

Immediately after a colicky attack there was a large amount of pus in the urine; this was followed by relief. The urine never appeared cloudy except following an attack. At cystoscopic examination the left ureteral catheter entered for a distance of about 4 cm., and pus did not come from the stump on withdrawal of the catheter; this showed that there was no infection of the portion of the left ureter remaining after its incision at the time of hysterectomy. It was impossible to find the orifice of the transplanted ureter. The abdomen was opened, and many adhesions were found between the intestines and the abdominal wall; the omentum was adherent to the bladder at one point. All of the adhesions were freed, and on the upper left quadrant of the bladder the transplanted ureter was found extending across the pelvis for a distance of about 7.5 cm. At the point where the ureter left the pelvic wall below the brim of the pelvis, it was buried in dense scar tissue. The ureter was resected close to the bladder, and the remaining stump cauterized and inverted into the bladder. Due to the scar tissue, it was difficult to dissect the buried portion of the ureter. The remaining part of the ureter lying along the muscle bed was easily traced to its termination and resected. The part of the ureter resected was about 18.75 cm. long. It was contracted near its juncture with the bladder, where there was a portion of thin-walled dilatation. Within the cavity was thin purulent material which contained colon bacilli and staphylococci.

Stricture.—Campbell [26] stated that faulty drainage is the cause of infection of the urinary tract in infants as well as in adults. In 2,420 children coming to necropsy at Bellevue Hospital, ureteral blockage was found in 47 (approximately 2 per cent). Urinalysis or postmortem examination revealed infection in four fifths of these. In a large number of children with chronic pyuria, ureteral obstruction was found as the underlying lesion. Most of these acute renal infections ended favorably within two or three weeks, but there was a large group which resisted all forms of treatment.

Campbell reported a series of seventy-four cases of ureteral obstruction in infancy and early childhood. He used the classification of intra-ureteral or extra-ureteral, since these characteristics determine to a large degree the type of surgical procedure. The chief obstructions of and within the ureter itself were found to be strictures, including the formation of valves, calculi, kinks and anomalous conditions. Strictures, whether congenital or acquired, were the predominating ureteral obstructions in infancy. Congenital strictures were not infrequent and occurred at the two ends of the ureter, the ureteropelvic or uretero-

26. Campbell, M. F.: Ureteral Obstruction in Infancy, Am. J. Surg. **5**:445, 1928.

vesical junctures. In twenty-two patients, the blockage was bilateral; this condition was found in one instance in a 7 months' fetus. Campbell expressed the belief that the formation of stone is favored by urinary stasis and is most often associated with obstruction. Obstruction by acute ureteral angulations was associated with nephroptosis and renal ectopia, usually occurring at or near the ureteropelvic juncture. This type of blockage was characterized by marked hydronephrosis above and a relatively normal ureter. In cases of complete reduplication, obstruction rarely occurred at the point the ureter crossed in the pelvic cavity just above the bladder. Abnormal ureteral insertion may be found high in the renal pelvis with marked angulation or a lip valve which obstructs drainage. There may be ectopic insertion into the bladder, urethra, vagina or rectum.

Extra-ureteral masses were found to be predominantly inflammatory or neoplastic. Aberrant vessels usually passed from the lower renal pole to the aorta or vena cava. Chronic pyuria and pain in the loins were the usual symptoms.

The chief symptoms were hematuria, urinary frequency, dysuria, ureteral colic or dull aching in the loins with or without radiation. Chronic pyuria was the most constant symptom. In some cases palpation may reveal a renal mass, varying markedly in size. The onset may be acute and often follows an acute focal infection, but the urinary infection does not clear up within the usual time. In some cases pyuria was noted from birth, and in a few congenital ureteral obstruction with associated infection was noted at necropsy. The degree of obstruction is largely reflected by the temperature and pyuria.

Obstructive urinary lesions are characterized by dilatation, infection and renal destruction. Dilatation was usually more marked above the point of obstruction, but the inflammatory type was not infrequently observed below this point.

Relief of obstruction is the object of treatment. Dilatation of ureteral strictures afforded marked clinical improvement but bacteriologic cure was obtained in only three of Campbell's cases. He stated the belief that clinical improvement resulted from dilatation rather than lavage. Water in abundance is prescribed as the best medicine, and alkalis are of value when they promote diuresis. Medical measures are of value only when used with surgical procedures to relieve the obstruction. Early recognition and treatment save extensive renal destruction and often years of suffering or early death.

BLADDER

Tumors.—Hunt [27] stated that difficulty in evaluating reported results in favor of various methods of treating malignant tumors of the bladder

27. Hunt, V. C.: The Surgical Treatment of Malignant Tumors of the Bladder, J. A. M. A. **91**:1704 (Dec. 1) 1928.

is due to the lack of uniformity in classifying them according to the type of lesion, the degree of malignancy, and the situation and extent of involvement.

He found epithelioma, with varying degree of malignancy, in 95 per cent of the cases. Regardless of the site of the lesion, in a series of 480 epitheliomas graded on a scale of 1 to 4, 10 per cent were graded 1 (least malignant), 32 per cent were graded 2, 35 per cent were graded 3, and 23 per cent were graded 4, making a total of 58 per cent of a high degree of malignancy. The epitheliomas of the base of the bladder tend to be more highly malignant than those of the lateral wall or the dome. If all other conditions are equal, 10 per cent better results may be expected in the treatment for epitheliomas of the lateral walls and dome, simply because of the degree of malignancy.

The time of beginning treatment was found to have a significant bearing on operability and on the results of treatment. In a series of fifty-one cases in which the condition was too far advanced for any form of treatment, it was found that the average duration of symptoms previous to medical treatment was almost two years. Bumpus reviewed a series of 212 cases in which radium alone, or radium in conjunction with some other forms of treatment, was employed. He concluded that the use of radium alone is not successful in cases in which other methods of treatment cannot be used, that poor results are obtained when radium treatment is followed by operation, and that radium is most useful in connection with fulguration or operation. Hunt considered cautery excision as the method of choice for tumors of the lateral and posterior walls and dome of the bladder. Recurrence at the primary site of the lesion is less likely to follow.

The mortality rate of surgical procedures depends on the site of the tumor, the magnitude of the operation and, in lesions of the base of the bladder, on the method of disposing of the ureter. The mortality is lowest following the excision types of operation employed in the lateral walls and dome, and highest in segmental resection for tumors of the base with reimplantation of the ureter. Division and ligation of the ureter has proved the best method if the ureter is involved in the lesion or in extensive operable tumors of the base. In approximately 370 cases of epithelioma of the bladder, the results were dependent on the site of the tumor, the extent of the involvement and the degree of malignancy. In general, about 65 per cent of the patients with lesions graded 1 or 2 are living and well three years after operation, while 35 per cent of those on whom the radical operation was performed for lesions graded 3 or 4 showed equally good results. Approximately 73 per cent of the patients having tumors of the lateral walls or dome graded 1 or 2 and 42 per cent having tumors graded 3 or 4 are living three or more years afterward; 50 per cent of those having lesions

in the base graded 1 or 2 and 25 per cent having lesions graded 3 or 4 lived without recurrence for the same period.

Aschner [28] stated that several factors are responsible for the fact that vesical neoplasms are regarded as different from tumors elsewhere in the body and not subject to the usual mode of classification. There is a tendency for benign papillomas to implant themselves in other parts of the bladder and in the suprapubic wound after open operation, and also for new tumors to develop after the original tumor has been destroyed. Patients with papillomatosis or those who have been cured of papilloma may later have frank carcinoma of the bladder or metastatic phenomena with a malignant clinical course, and rare cases of papilloma with typical benign cell structure may show infiltration of the wall of the bladder.

The ordinary variety of papilloma is a soft, shaggy, villous tumor arising from the mucosa of the bladder by a well defined pedicle. The skeleton is formed by a delicate connective tissue core continuous with the submucosa of the bladder and containing blood vessels. The noninfiltrating type of papillary carcinoma may be pedunculated or sessile. It is usually indistinguishable cystoscopically or grossly from benign papilloma, from which a large percentage probably develop. The cell changes which indicate a malignant condition may be slight and limited to a small part of the growth, or marked and present throughout the growth. Nonpapillary carcinomas are characterized by their tendency to spread downward into the wall of the bladder and laterally under the normal mucosa, and often by ulceration and necrosis at the center of the growth. They seem to arise from the deeper cells of the mucosa, nests of which are not infrequently seen dipping downward in inflammatory processes, especially at the trigone and vesical neck.

Aschner concluded that in 97 per cent of the cases cystoscopic biopsy furnished the most reliable information as to the nature of tumors of the bladder. The failures occurred in multiple tumors and in papillomatosis. Prognosis cannot be made from biopsy alone in cases of malignant disease. The use of radium or operation, except on a debilitated patient, is indicated when a diagnosis of malignant disease is made in a case simulating papilloma. Aschner stated the belief that tumors of the bladder are benign or malignant, and that they may be classified in a manner harmonious with general tumor and clinical terminology. He did not consider cell grading alone as practicable for clinical purposes, and prognosis on such a basis does not coincide with the late results in his series of cases. Infiltration appears to be a more reliable guide to the extent of the lesion, and the site of the malignant tumor determines its resectability and influences prognosis materially.

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28. Aschner, P. W.: The Pathology of Vesical Neoplasms: Its Evaluation in Diagnosis and Prognosis, J. A. M. A. **91**:1697 (Dec. 1) 1928.

The surgical procedure of choice when a diagnosis of carcinoma is made by biopsy is resection of the whole thickness of the wall of the bladder. Failure to do so, even in the case of pedunculated tumors, has often resulted in recurrence. Stalk invasion and tumor cells in blood vessels at the base cannot be detected by gross inspection. Only 20 of 137 papillary carcinomas were not infiltrating. Aschner expressed the belief that biopsy should always be made before radical operation on the bladder is undertaken, as other lesions may closely resemble neoplasm.

Stone.—Cabot [29] classified the cases of complicated stone in the bladder as cases in which the bladder is the seat of some other condition requiring surgical treatment. One of his fundamental principles when studying a patient with stone in the bladder is to determine whether there exists in the bladder some condition other than lithiasis which requires surgical treatment. If there is obstruction, diverticulum or other abnormality, the treatment for the stone becomes secondary to that for the other lesion.

Stone in the bladder may be treated by incision or by crushing and evacuation by instruments. Litholapaxy is the method of choice when it can be carried out satisfactorily. Indian surgeons are unanimously in favor of litholapaxy because convalescence is shortened, shock is lessened, and suprapubic scars are avoided. Cabot stated that there are several contraindications to litholapaxy. It should not be performed when there is disproportion between the size of the stone and the capacity of the bladder. When a large stone lies in a more or less contracted bladder, the movements of the instrument are limited; the amount of trauma resulting from many fragments is considerable and the time consumed in the operation, even if it is successful, is of disadvantage to the patient. In general a bladder that holds less than 125 cc. and contains a stone of considerable size will not be suitable for litholapaxy. Great surgical skill and experience may definitely modify this statement. Cabot considered the second contraindication to be cases in which the stone has as its nucleus a metallic foreign body or other substance which cannot be crushed. Before the development of the roentgen rays, it was difficult to determine with certainty the nature of the foreign body previous to operation. Litholapaxy should not be performed if the necessary instruments cannot be passed through the urethra. Stricture of the urethra is not a contraindication, since it can be readily divided by internal urethrotomy.

The group of borderline cases includes some of those in which the stone has a foreign body as its nucleus and a group in which the stone

29. Cabot, Hugh: The Principles of Treatment of Stone in the Bladder, J. A. M. A. **91**:1968 (Dec. 22) 1928.

lies not in the bladder but in a more or less dilated prostatic urethra. Some of the latter group may be considered as possibly satisfactory subjects for litholapaxy.

Diverticula.—Lower and Higgins,[30] from a study of the literature and their own experience, noted that the walls of diverticula vary in thickness, generally increasing with progressive inflammation of the diverticulum, although there may be a variation in different portions of the same diverticulum. The most common site of diverticula is proximal to one of the ureters, but no region of the bladder is exempt. Durrieux found records of fifteen diverticula situated in the trigone. Because of the quantity of fluid they contain, large diverticula tend to force their way backward, generally along the line of least resistance. Small diverticula usually lie between the bladder and rectum and, as they increase in size, extend laterally and upward. As a rule the orifice is quite small and entirely out of proportion to the size of the sac. The difficulty in emptying this type of diverticula makes them resistant to palliative treatment. The ureter may open directly into the diverticulum or may be incorporated in the wall of the diverticulum itself.

Diverticula are relatively infrequent in women. Rose's explanation of this is that in the female bladder, due to the absence of prostatic and seminal vesicle fixation, there is less loss of elasticity and less opportunity for diverticula to develop. Rathbun holds that all true diverticula are congenital and that the so-called acquired diverticula are only "exaggerated trabeculations." Diverticula may occur at any age, but they usually occur after the age of 50, during the period of prostatic obstruction.

The most common complications of diverticula are infection, calculi and tumors. Stagnation and infection are naturally conducive to the formation of stones, and these factors are usually present in varying degrees in such cases. Calculi in the diverticulum may be single or multiple. If they are multiple they may become faceted and lie close together, so that only the roentgen rays will show that more than one stone is present. When large stones are found in the diverticulum, they are usually associated with lithiasis in the bladder.

Diverticula do not cause definite symptoms, and the clinical picture varies with the presence or absence of infection. Many diverticula are discovered in cystoscopic examination in cases in which their presence has not been suspected, especially in hypertrophy of the prostate gland. The following diagnostic technic is used: Cystograms are made under the fluoroscope. After the bladder has been catheterized and drained, it is refilled with a solution of sodium iodide. A solution of from 10 to

30. Lower, W. E., and Higgins, C. C.: Diverticula of the Urinary Bladder with Report of One Hundred and Ten Cases, J. Urol. **20**:635, 1928.

17 per cent may be used without apparent irritation of the bladder. As the bladder is gradually filled, a close watch is kept for the appearance of irregularities which might be caused by hypertrophy of the prostate, tumors of the bladder, trabeculations or diverticula.

The present trend of treatment for diverticula is toward radical excision of the entire sac. As diverticula are usually associated with obstruction, the cause of the latter must also be removed in order to secure a satisfactory end-result. Lower operates under spinal or sacral anesthesia; in the case of an apprehensive patient, he adds analgesia with nitrous oxide and oxygen. A median suprapubic incision is made and carried down to the bladder. After the peritoneum is stripped back, the bladder is opened. Exposure of the interior of the bladder is secured with flexible retractors and a Cameron light. The diverticulum is located, and from its size and position the mode of procedure is determined. If the extravesical approach is used, the collapsed diverticulum is first converted into a solid or semisolid tumor by packing it with a gauze tape. Lower then dissects down outside the bladder, severing the attachment of the diverticulum and closing the opening into the bladder. It is important that the closure of the bladder at the point of removal of the diverticulum be made with good muscular apposition, the walls being inverted if possible so as to leave a slight ridge on the inner surface of the bladder rather than a depression at the point from which the attachment of the diverticulum was removed. Such a depression might serve as a starting point for recurrence of the diverticulum.

In forty-five cases of the series, the diverticulum was excised. There were three operative deaths (7 per cent). Twelve of the patients have not been traced since operation. Five patients have died since operation. Of the remaining twenty-one patients, observed for periods varying from six months to fourteen years, the average postoperative period was four years; marked improvement was noted in twelve; in nine, there was complete relief of symptoms.

Prognosis is usually favorable if radical operation is performed early and before renal impairment has become marked. In cases in which a malignant growth is present, the prognosis must be guarded.

Fistula.—Farman and Thompson,[31] before attempting an operation for a vesicovaginal fistula, follow the principle of correcting any cystitis or other intravesical complication. Such a procedure presupposes a thorough cystoscopic examination of the bladder, determination of the exact size and situation of the fistula, and its relationship to the ureters. Small fistulas involving the lower part of the vesicovaginal septum

31. Farman, Franklin; and Thompson, R. C.: Vesicovaginal Fistula: Etiology, Surgical Principles of Repair and Technique of Suprapubic Transvesical Operation, J. Urol. **20**:663, 1928.

usually are more readily accessible and lend themselves better to proper dissection and closure by the vaginal operation or one of its modifications. Fistulas high in the vagina are difficult to close, and failure is frequent by the vaginal route.

In repairing vesicovaginal fistula, a proper exposure of the operative field is made, as success depends on accurate and complete closure with well placed sutures in healthy tissue. All scar tissue is dissected from the thick vesicovaginal septum until the denuded, raw surfaces are soft and plastic. This will usually leave an opening two or three times the size of the original fistula to be closed by suture. Mobilization of the bladder is one of the most significant steps in the technic of repair; it permits the viscus to return to a more normal position (retraction upward and forward), and tends to separate the opening in the bladder from the opening in the vagina. It is necessary to secure a tight nonleaking closure that is urine proof. The method of suturing should be adapted to the size of the openings, elasticity of the tissues and accessibility. Circular, purse-string, lockstitch or continuous through-and-through sutures may be used. Chromic catgut generally is required for the main sutures. Opinion varies as to the necessity, method and length of time advisable for drainage of the bladder during healing. The majority of surgeons using the vaginal route for repair have drained the bladder after from six to ten days with a Pezzer catheter. A few have performed suprapubic cystostomy. The idea of drainage by catheter or cystostomy is to immobilize, during healing, the previously mobilized floor of the bladder and to relieve pressure on the line of suture.

The success of operation depends partially on skilled postoperative care, for any complication may be the undoing of the repaired fistula. Infection of the part usually means failure, but it is well known that tissues in this region possess a high degree of healing properties and local resistance. It is important to prevent spasm of the bladder, unnecessary movement or straining, restlessness, constipation, and contamination of the pelvic parts. Mayo and Walters expressed the belief that the success of repair depends on healing in the line of suture and accurate closure of the openings in the bladder and vagina. Some operators suture the openings at right angles to each other.

Paralysis.—Cahill [32] observed that in conditions causing paralysis or destruction of the spinal cord, retention of urine began at once and continued until the bladder was greatly distended and showed in the lower part of the abdomen as a large ovoid tumor. The bladder still retains the power of contraction and should be properly stimulated so that it will gradually assume the power automatically to relieve itself.

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32. Cahill, G. F.: Treatment of Bladder Paralysis Due to Non-Tabetic Spinal Cord Lesions, Am. J. Surg. **5**:442, 1928.

In treating patients with paralysis of the cord with resulting urinary retention, Cahill does not perform catherterization but allows the bladder to fill for twenty-four hours and then forces the relief of the bladder by pressure excited on the fundus. When the bladder can be clearly and easily felt, the right or left hand is placed sidewise across the fundus and the ulnar side pushed above the fundus as far as possible into the abdomen. The fundus is then cupped or grasped and pressure exerted by pushing down against the pelvic opening. The urine may not appear for one or two minutes after pressure and then may be voided only in a small irregular stream. Pressure is then applied every two hours, each time the amount of urine obtained slowly increasing and the pressure required decreasing. It usually takes from six to ten days before the bladder empties well behind the symphysis and several weeks before it empties completely. If possible, Cahill instructs patients how to apply the pressure themselves, and sometimes they are able to hasten the emptying of the bladder by applying their own increase of abdominal tension by breathing.

If there is infection, catheterization is instituted but only until the infection has subsided.

Cysts.—Altmann [33] stated that cysts of the posterior wall of the bladder, especially in the prostate gland, are comparatively uncommon. Eliminating echinococcus and dermoid cysts, Meyer considered the following as etiologic possibilities: (1) fetal inclusion of the prostatic utricle due to epithelial adhesions, that is, a sealing off of the terminal portion with a subsequent cystic dilatation of its lumen as well as a disturbance in the development of the mullerian duct; (2) cystic dilatation of the prostatic and trigonal glands; (3) abnormal persistence of portions of the mullerian duct derived from its terminal segment, and (4) offshoots from the seminal vesicles and ducts. On account of the frequent association of the cysts with the utricle, Altmann favored the first hypothesis. Hypotheses regarding the association of neighboring glandular structures may be assumed. The second group comes in this classification.

A case of a man, aged 19 years, is cited which could be classified in the third or fourth group. Necropsy revealed marked hydro-ureter and hydronephrosis on the left side, associated with the seminal vesicles and vas. A large piece of adjacent tissue and wall of the bladder was removed in order to study the case thoroughly. The inner wall of the cyst was composed of a double layer of cubical epithelial cells. The cyst was entirely closed off from adjacent tissues.

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33. Altmann, Franz: Zur Kenntnis der Cysten an der hintern Blasewand beim Manne, Ztschr. f. urol. Chir. **24**:438, 1928.

There are only nine reported cases in the literature, in all of which the cysts were small, about 2 cm. in size, and were found at varying ages, from birth to old age. Six were in the median line just above the prostate gland, and three were situated below the prostate gland and medially to the vas. Most of the cysts were oval or pear-shaped. Histologically, all cysts were lined with cubical epithelium. In two cases, including that of Altmann, muscle fibers were found in the wall of the cyst. This was interpreted as meaning an association with the ductus deferens.

Exstrophy.—Judd and Thompson [34] stated that the ultimate cause of exstrophy of the bladder is not known, but the existing theories collectively purpose that it results from mechanical rupture, pathologic lesions, or defective embryonic development. Histologic studies reveal that the structure of the bladder in cases of exstrophy is usually unlike that of the normal bladder, and glands have been constantly observed. There are usually varying degrees of local inflammation, the result of mechanical and chemical irritation and infection. Associated ascending infection is common, and death usually is caused by toxemia of infection or of renal insufficiency.

Judd and Thompson described 2 cases of carcinoma complicating exstrophy of the bladder, making a total of 20 reported cases. Adenocarcinoma was reported in 15 cases and squamous cell carcinoma in 2; a histologic report was not made in 3 cases. Although adenocarcinoma is of comparatively rare occurrence in the normal bladder, it is the type which most commonly occurs in exstrophy of the bladder. Nineteen (2.19 per cent) adenocarcinomas were found among 867 tumors of the normally developed bladder at the Mayo Clinic. Of the 20 reported cases, 12 occurred in men and 7 in women; in 1 case, the sex was not mentioned. Two occurred in the third decade, 5 in the fourth, 9 in the fifth, 3 in the sixth, 1 in the seventh. Surgical treatment was employed in 10 of the 20 cases. In 3, simple extirpation of the bladder was performed. In 1 case, transplantation of the ureters by the Mayo method preceded removal of the bladder. The patient died two years after operation from metastasis. In 2 cases cited by Judd and Thompson, the patients are alive and well three, and six and a half years respectively, after operation. In 3 other cases transplantation of the ureters into the colon was performed. One of the patients died eight days later from uremia following ascending renal infection. In the other 2 cases, resection of the bladder was performed secondarily.

Vesical Neck.—Herbst [35] observed that although the symptoms of fibrosis of the neck of the bladder may not be marked until adult life

34. Judd, E. S., and Thompson, H. L.: Exstrophy of the Bladder Complicated by Carcinoma, Arch. Surg. **17**:641 (Oct.) 1928.

35. Herbst, R. H.: Fibrosis of the Vesical Neck, J. A. M. A. **91**:1614 (Nov. 24) 1928.

or later, a surprisingly large number of these patients give a history of disturbances of the bladder in childhood.

The appearance of the bladder, as well as the symptoms of fibrosis, is quite different from that found in other obstructive conditions. Fibrosis of the vesical neck is generally characterized by a small contracted bladder with massive thickening and hypertrophy of the wall, instead of a large dilated bladder with moderate hypertrophy of the muscle coat. The symptoms of fibrosis may be classified as those referable to the bladder and those produced by changes in the upper urinary tract. The bladder is usually small and often contracted because of the hypertrophy of the muscular wall, a condition which frequently causes an active form of incontinence, in contrast to the passive overflow type seen in other forms of obstruction. Urgency and frequency of urination are prominent symptoms. Complete retention is infrequent due to the powerful contraction of the hypertrophic wall of the bladder, but regurgitation to the upper urinary tract is more pronounced than in most other types of obstruction. On rectal examination, the prostate gland is usually about normal in size and in consistence. If an instrument is introduced into the bladder, resistance may be encountered immediately at the neck of the bladder, which as a rule is easily overcome. In uncomplicated cases there is marked trabeculation, the trabeculae being heavy with deep cellules between them. The vertex of the bladder is more contracted than the lower part, causing the formation of a dome which at times may be mistaken for a diverticulum.

Herbst stated the belief that the degree of retention and the impairment of the renal function should be determined so as to distinguish between the cases of fibrosis in which the condition can be corrected without drainage and those in which drainage is required. He considered some type of drainage by catheter to be preferable to preliminary cystostomy because of the difficulty encountered later in obtaining good exposure of the neck of the bladder, which is essential to thorough removal of the fibrotic neck. Some form of transurethral or punch operation is the method of choice in the milder types of fibrosis, particularly those in which the lower segment of the internal urethral orifice is most involved.

Mucous Glands.—Edelman [36] reported two cases from Mount Sinai Hospital in which intestinal-like mucous glands were found in the urinary bladder. Both patients complained of frequency, dysuria and hematuria, suggestive of new growth or intense cystitis. One gave a history of having passed gravel.

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36. Edelman, Leo: Muciparous Glands in the Mucosa of the Urinary Bladder, J. Urol. **20**:211, 1928.

Some observers deny that mucous glands exist in the urinary bladder; others admit their presence; others interpret them as aberrant prostatic or urethral glands. The cases reported in the literature showing lesions containing "intestine-like" mucous glands have their origin ascribed to misplaced embryonal intestinal glands, to embryonal rests, to proliferation and metaplasia of the surface epithelium (Enderlen), to proliferation of lesions in cystitis cystica due to an inflammatory process (Stoerk and Zuckerkandl), and to proliferation of mucous glands normally present in the mucosa (Bridoux).

The lesions do not cause distinctive symptoms. The patients usually complain of frequency, dysuria and hematuria. Therefore, the diagnosis can be made only by microscopic examination of the tissues removed. The treatment is either excision or destruction with the cautery. The persistence of these glands may possibly be the basis for the development of adenoma or adenocarcinoma.

PROSTATE GLAND

Hypertrophy.—Davis [37] summarized the immediate and later results in a series of 176 consecutive cases in which perineal prostatectomy was performed under sacral anesthesia in an attempt to determine the immediate mortality and the percentage of satisfactory functional results. There were 3 deaths (1.7 per cent) in his series. The average age of the patients was 70; 16 were more than 80 years of age, two of these being 88.

Davis stated that the factors instrumental in reducing the mortality rate of prostatectomy are preliminary drainage, sacral anesthesia and careful hemostasis. Good hemostatic control is particularly important, as many deaths may result from hemorrhage due to infection secondary to lowered resistance. Prostatectomy may be made an almost bloodless procedure as the result of the opportunity for deliberateness in controlling individual bleeding points by suture and ligature which is afforded by the employment of sacral anesthesia, and the use of an inflated hemostatic bag to control hemorrhage during the first few postoperative hours. The anesthesia used in all of Davis' cases was sacral block, including injection through the sacral hiatus (caudal anesthesia), as well as through the first, second and third sacral foramina on either side. This type of anesthetic has eliminated the problem of anesthesia for prostatectomy in old and debilitated patients. It is easily and simply administered, is almost uniformly efficient, and does not cause complications. There was not a death nor a reaction of consequence in his entire series. Hemorrhage should be treated as an

37. Davis, Edwin: Perineal Prostatectomy Under Sacral Anesthesia, J. A. M. A. **91**:1618 (Nov. 24) 1928.

emergency measure and should be checked by mechanical means, even though it necessitates a secondary operation.

Davis expressed the belief that functional results should be as significant, if not more so, than the immediate mortality rate. Good functional results are dependent on accuracy in preoperative diagnosis as well as on proper operative technic. On the basis of his late observations and on the assumption that there has been a proper diagnosis, preparation and operative technic, Davis made a conservative estimate that one may expect 80 per cent of satisfied patients following prostatectomy and 15 per cent of fairly satisfied patients.

Lewis [38] employed perineal prostatectomy exclusively for several years, but for the last fifteen years he has obtained better results with the suprapubic method. He pointed out that, even though Davis had a low immediate mortality rate in his series, in 36 of 100 patients traced the condition remained uncontrolled, while six cases of fistula resulted. He believed that these should not have been present in any of the cases in which prostatectomy was performed.

Thomas,[38] stated that the mortality rate of Davis will not be improved for a long time. He expressed the belief that Davis should not be permitted to convey the idea that in all cases of prostatic hypertrophy operation should be performed by the perineal route. If those who practice this method exclusively would give more attention to the route and make the type of operation dependent on the pathologic changes present, not only would the present mortality rates be lowered but improvement would attend the morbidity results. It is Thomas' belief that there is something wrong with urology when some of the leading exponents contend that prostatectomy should always be done suprapubically, while others insist that it should be done perineally.

Livermore [38] has favored the suprapubic method of prostatectomy because he has obtained better results and considers himself more skilled in it. It is his opinion that the choice of technic is a personal matter.

Foley [38] stated the belief that it is useless to attempt a comparative appraisal of perineal and suprapubic prostatectomy because of the prejudice of advocates of the two operations. He considers perineal prostatectomy a technically difficult procedure, the main difficulty being the proper division of the recto-urethralis muscle. If technical faults on the part of the operator are not considered, the perineal operation regularly gives a functional result as good as it is possible to obtain by the suprapubic approach. A poor functional result means an incorrect dissection. To him there is no latitude between the proper dissection which will give a perfect functional result and an improper one resulting in incontinence or injury to the rectum.

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38. In discussion on Davis (footnote 37).

Carcinoma.—Roberts [39] reported three cases of carcinoma of the prostate. In the first case he found metastasis to the skull, the left clavicle, the left fifth rib, and the abdominal lymph drainage limited to the pelvic vessels. The outstanding features of the second case were the involvement of the upper dorsal vertebrae and the fourth left rib, together with the absence of any involvement of the abdominal lymph vessels above the level of the second lumbar vertebra.

A study of these cases, together with others of a similar nature showing involvement of the skull and upper dorsal region, suggested the possibility of a constant path of dissemination from the primary growth in the prostate gland. On theoretical considerations the spinal canal was regarded as a possible route, and it was further indicated by the widespread involvement of the pelvic bones sometimes seen in these cases. It was therefore decided to examine the spinal column in all cases in the future. In Roberts' third case, necropsy serves to support the contention. At necropsy the spinal laminae, with the ligaments, were removed in one piece from the cervical to the lower lumbar region, and at once plaques of growth were seen to involve the whole length of the ligamenta subflava and the intraspinal surface of the laminae. Both the dura mater and its contents and the posterior common ligament appeared to be normal. There was an almost continuous direct spread of growth on the intraspinal surface of the dorsal wall of the spinal canal from the sacral to the cervical region, whereas the abdominal lymph spread had extended only as far as the upper lumbar region. It is interesting to note that the thoracic duct was uninvolved throughout its thoracic course. Histologic section of the temporal bone showed marked invasion by carcinoma cells of the same types as those found in the pelvic lymph glands and prostate gland. A section of the lamina in the upper dorsal region also showed columns of carcinoma cells in the spaces of the connective tissue of the ligaments and periosteum of the laminae; some of these columns appeared to be surrounded by a layer of endothelial cells suggesting lymph vessels, while others appeared to lie in close contact with the connective tissue fibers and cells. The spinous process and lamina were also extensively involved.

Roberts discussed the usual methods of the spread of metastasis and suggested that another route plays an important (and perhaps the most important) part in the distant dissemination of malignant cells from the prostate gland. This path consists of the lymphatic vessels and tissue spaces of the spinal laminae with their associated ligaments. Structurally, the ligamenta subflava consists of elastic tissue fibers with a network of lymph spaces both between and on the surface of the fibers

39. Roberts, O. W.: Some Notes on Carcinoma of the Prostate; Including Evidence of an Intraspinous Route of Dissemination, Brit. J. Surg. **15**:652, 1928.

of which they are composed; also, the interspinal ligaments have loose connective tissue between the fibrous framework. The path by which the cells reach the spinal canal is at present unknown, but in a recent postmortem examination two likely pathways were noted. One path is by the lymph drainage of the prostate gland to the sacral lymph glands; these glands lie near the anterior sacral foramina and, in this case, were found to be extensively invaded. It is possible that permeation of lymph vessels by the carcinomatous cells may obstruct the flow of lymph from the sacral glands to the iliac and para-aortic vessels and may lead to an increase of flow through the vessels linking up the intraspinal with the intra-abdominal lymph vessels. Along this path, the malignant cell would be able to grow and permeation or emboli occur readily. The other path noted was the loose connective tissue lying on the surface of the levator ani and coccygeus muscles; a tongue of new growth was found passing from the prostate gland toward the anterior sacral foramina in this tissue. Histologically, the growth appeared to be due to infiltration of loose tissue rather than to lymphatic permeation, but further sections are necessary before this question can be decided. The pelvic nerves appeared to be free from invasion, as did the blood vessels. By this intraspinal route, rapid dissemination to distant parts of the body is feasible. The vertebrae, ribs and skull are accessible to the invading cells, and the involvement of the bone-marrow of these bones may account for the extreme anemia and asthenia in cases in which metastasis is so widespread. Theoretically, one would expect changes in the lymph flow in the upper dorsal region, since the main lymph vessel and its branches in this region are subject to the suction action of the respiratory movements of the thorax and of the negative pressure in the great veins. In this way permeation of vessels in the upper dorsal region, especially of the left side, would be explained.

Wildbolz [40] operated on forty patients with carcinoma of the prostate. Three (7.5 per cent) of the patients died from the operation; thirteen (30.2 per cent) had either multiple metastasis or local recurrence from eighteen months to three years after operation; four died from one to three years after the operation of other diseases, without evidence of malignant recurrence; twelve lived more than three years after the operation, and were completely free of the trouble and without evidence of recurrence; these might be said to have had an operative cure. One patient died of pneumonia nine years after operation, two died of heart trouble six years after operation, and one died of apoplexy five years after operation. Five patients were completely well at the time this paper was written, more than three years after operation. In all of these cases, the diagnosis was made by histologic examination.

40. Wildbolz, Hans: Die Erfolge operativer Therapie des Prostatakarzinoms, Schweiz. med. Wchnschr. **58**:726, 1928.

TESTES, EPIDIDYMIS AND SEMINAL VESICLES

Carcinoma.—Scholl [41] reported the case of a man, aged 22, who came for relief of pain in the right inguinal region and because of swelling of the right testis, which had been severely injured while he was playing football fourteen months before. For six months there had been a gradual swelling of the right side of the scrotum, until it was about twice its normal size. The testis was smooth, rounded and slightly larger than normal. The epididymis could be identified easily; it was distinctly separate from the testis and markedly enlarged.

At operation the testis was not increased in size and apparently was not diseased; it was smooth, rounded and a normal bluish white. The epididymis was greatly enlarged and irregular in contour. It was readily separated by sharp dissection from the testis. There was no invasion of the testicular substance, which was normal in size, shape and consistence. The epididymis was nodular and reddish. The vas was separated and a short segment removed with the epididymis. Microscopic examination revealed the growth to be malignant and the testis, the surrounding coverings and the cord were removed. Three months after operation, a mass 2 cm. in diameter was found below the lower angle of the incision. At a second operation, the fascia of the external oblique muscle was opened and the stump of the cord excised at the internal ring. The cord, tumor and all the surrounding tissues, including the inguinal glands and subcutaneous tissue, were then removed. Enlarged inguinal glands were not found. The wound healed well, and the patient was given roentgen treatment over the lower portion of the abdomen and the area of recurrence.

Four months after the operation the patient became short of breath and cyanotic. Examination revealed a large amount of fluid in the right side of the chest. A needle was inserted into the base of the left pleural sac, and 4 liters of blood-stained fluid was withdrawn. Roentgen examination of the chest after removal of the fluid revealed a mass about 6 cm. in diameter in the region of the hilum of the lung. One week later a second tapping was done, and 2 liters of fluid was removed. After that the patient's chest was tapped about once every ten days, from 2 to 3 liters of fluid being removed at each tapping. The pathologist's diagnosis was adenocarcinoma of the epididymis.

Tuberculosis.—Young [42] presented an analysis of twenty-two cases of genital tuberculosis in which he operated at least five years ago. In six cases nephrectomy was carried out in addition to the radical removal

41. Scholl, A. J.: Primary Adenocarcinoma of the Epididymis: Report of a Case, J. A. M. A. **91**:560 (Aug. 25) 1928.

42. Young, H. H.: Brief Note on Ultimate Results of Radical Operation for Tuberculosis of the Seminal Tract, J. Urol. **19**:679, 1928.

of the seminal tract. In several of these cases, severe urinary symptoms with involvement of the seminal vesicles and epididymis had developed in the tuberculous process. In most of the cases the condition of the patient was poor, with local involvement extending to the seminal vesicles and the prostate gland, as well as to the epididymis on one or both sides and sometimes to the testes. In five of the early cases only one seminal vesicle and one lobe of the prostate gland were removed, along with one side of the epididymis and one vas. Recurrence of tuberculosis in the remaining side of the epididymis has led Young to practice bilateral vesiculectomy and ampullectomy in cases of this type, with markedly improved results in eliminating subsequent involvement of the remaining epididymis. The prostate gland was involved close to the urethra in most of the cases. In four patients a persistent urinary fistula was present, leakage occurring only during urination, indicating that it came from the prostatic urethra and not the bladder. Patients were greatly relieved of pain, frequency of urination and hematuria by the operation of removal of the tuberculous seminal tract, even when pulmonary tuberculosis was present and was the cause of death. In five of six cases in which both vesiculectomy and nephrectomy were done, pulmonary lesions were present but at the last report only one patient had died.

In regard to operative technic, Young has found the use of caudal anesthesia usually successful in securing a painless procedure until the deep portions of the seminal vesicles and vas are attacked, and then local infiltration anesthesia is usually satisfactory in relieving pain.

There were no operative deaths. Six deaths are known to have occurred during the five years or more since operation; all of these patients had pronounced pulmonary involvement before operation. Fourteen patients (67 per cent) have been traced and found in good condition from one to twelve years after operation (nine, more than five years; one, four years; three, three years and one, one year). Statistics show that seminal vesicles are involved in most cases of genital tuberculosis.

Barney and Colby[43] stated that genital tuberculosis takes its origin from either coexistent or healed extragenital lesions, which are usually found in cases of genital tuberculosis. In a large percentage of cases in which the epididymis is involved, clinical examination shows involvement of the prostate gland and seminal vesicles. There are two views as to the incipiency of this disease: that it is primary in the epididymis, and that it is primary in the seminal vesicles. The bacillus of tuberculosis may be transmitted from the epididymis to the seminal vesicle

43. Barney, J. D., and Colby, F. H.: The Treatment of Genital Tuberculosis in the Male, J. Urol. **19**:657, 1928.

with the stream of secretion, known as the "descending route," or the infection may follow the blood stream or "ascending route." Most writers favor the former route.

The lesions of the epididymis usually begin in the globus minor, and the seminal vesicle on the same side is the one usually involved. Possibility of involvement of the second epididymis is decreased by removal on the side first affected, and the excision of the vas on the apparently healthy side aids in curtailing the spread of the disease to that side. The testis may not become affected even after years of contact with a tuberculous epididymis.

Treatment may be surgical or medical. Radical operation involves the removal of the seminal vesicles, prostate, vas and epididymis, together with the testis if it is involved. Medical treatment may include minor operations but consists primarily of the administration of tuberculin, heliotherapy, roentgen rays and ultraviolet rays and does nothing more than arrest the progress of the disease in some instances, often without improving the general condition of the patient.

In the author's experience, epididymectomy resulted in as low an operative mortality and good results in general as the more radical operations. It has been frequently observed that following epididymectomy the disease found before operation in the seminal vesicles and prostate gland not only ceases to progress but actually retrogresses to the point of clinical cure. This observation gives support to the belief that the disease begins in the epididymis.

Many patients with genital tuberculosis eventually die of tuberculosis of the lung or of miliary tuberculosis, which is probably attributable to the original lesion in the lungs or bronchial lymph glands rather than to areas of disease which conservative operation or medical treatment has left behind.

Wildbolz [44] stated that acute tuberculous epididymitis is much more significant than is generally believed. In about 25 per cent of all the patients with tuberculous epididymitis that he saw the condition began with an acute period similar to that caused by infection with gonococci, colon bacilli or staphylococci. This acute onset occasionally leads to a false sense of security, and valuable time is lost. In order not to make serious mistakes, it is necessary always to remember that tuberculosis may produce acute epididymitis.

It is usually easy to distinguish acute tuberculous epididymitis from gonorrheal or other epididymitis. Acute tuberculous epididymitis is produced only in the presence of high allergy. This high allergy is only found if the patient has, at the moment, a virulent tuberculous infection,

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44. Wildbolz, Hans: Nonspecific Chronic Epididymitis and Tuberculous Epididymitis, Proc. Staff. Meet. Mayo Clinic **3**:169, 1928.

so that in most cases of acute tuberculous epididymitis tuberculosis of the bladder, kidney, prostate, seminal vesicles, lungs or joints will be associated. If the diagnosis does not seem clear, one must observe the patient a short time. In the case of gonorrheal infection or other infection, the infiltration of the epididymis will regress after a few days. In a case of acute tuberculous epididymitis diminution of the symptoms of acute inflammation will be noted, but the infiltration will not regress and will perhaps progress. This slow regression of infiltration must always be a warning that the epididymitis may be tuberculous.

In about 25 per cent of the cases the tuberculous infection is primary in the epididymis, and the epididymis should be removed. In more than 150 cases of epididymectomy which Wildbolz could trace for many years, there was no recurrence of tuberculosis of the testis when it was not present in the testis at operation. Wildbolz expressed the belief that the best way of preventing tuberculosis of the testis is removal of a tuberculous epididymis as soon as possible, and he does this even in the acute period of the infection. It is slightly more difficult to remove the epididymis in the acute stages, but the acutely inflamed epididymis can be detached and removed separately. As soon as it has been determined that the epididymis is tuberculous, either chronically or acutely infected, it should be removed at once. In 90 per cent of the cases, there will never be further passage of spermatozoa. Consequently, there is no reason for not removing it.

Wildbolz has tried the various conservative methods of treatment, such as tuberculin, roentgen rays and heliotherapy. Even after employing conservative nonsurgical methods for one or two years, he was not certain that the recovery was complete. He has removed the epididymis following treatment by conservative methods for from three to seven years, and has found many tubercles and virulent bacilli. He believes that in the reports of healing in cases of tuberculous epididymitis after roentgen or tuberculin treatment in a few weeks or months the condition was not tuberculous epididymitis but chronic nontuberculous epididymitis, a disease not yet universally known.

Seminal Vesiculitis.—Wassiljeff [45] stated that most of the literature deals only with the clinical diseases of the seminal vesicles and little with their pathologic anatomy. The seminal vesicles are often mentioned in association with various disease processes. Using the material from 120 necropsies, Wassiljeff attempted to determine the frequency of vesicle changes due to disease and age.

The collected material was divided into the following groups: six cases of syphilis (syphilitic mesa-ortitis with aneurysm and progressive

45. Wassiljeff, A. A.: Ueber die pathologischen Veränderungen der Samenblasen (auf Grund des Leichematerials), Ztschr. f. urol. Chir. **24**:502, 1928.

paralysis); ten cases of nonspecific diseases of the vascular system, arteriosclerotic and contracted kidney, and arteriosclerosis of the cerebral arteries; thirty-one cases of all types of tuberculosis, that is, of the lungs, kidneys, genital organs—acute, miliary and chronic; thirty-six cases of all types of acute and chronic septic processes, such as endocarditis and peritonitis, and also the acute infectious diseases; twenty-six cases of malignant growths of the various organs, and eleven cases of miscellaneous growths and diseases.

Changes in the seminal vesicles were grouped as follows: comparatively pure types of changes in the seminal vesicles due to age; changes which are on the borderline between those due to age and those due to pathologic conditions, and pure pathologic changes.

Wassiljeff stated that changes of the seminal vesicles due to age show themselves in thickening of the septums of the vesicles, in diminution of their lumen, in substitution of the muscle fibers by connective tissue, in deposition of pigment in the epithelial cells, and in complete atrophy of the vesicles. The vascular system of the seminal vesicle capsule is early affected with arteriosclerotic changes. Deposition of pigment in the cell elements of the walls of the vesicles and the formation of cystlike diverticula may also be attributed to changes due to age and is apparently aided by the cachectic diseases. The formation of cysts is probably instituted by inflammatory processes, increasing with the addition of connective tissue, and occasionally there may be obliteration of the lumen of the vesicle. Inflammatory processes were frequently found in the seminal vesicles, such as metastatic pus vesiculitis, chronic and acute catarrhal vesiculitis, chronic fibrous vesiculitis (dilated or atrophic vesicles) and chronic perivesiculitis.

Chronic inflammation of the vesicles was demonstrated in 47 per cent of the septic cases, in 80 per cent of the syphilitic cases, and in 19 per cent of the tuberculous cases. Tuberculous changes of the vesicles were found in 22.8 per cent of the cases of general tuberculosis. The calcification of the contents of the seminal vesicles results occasionally in cases of tuberculosis. In cases of malignant growths of the prostate gland and the bladder, infiltration of the walls of the seminal vesicles was observed. Metastasis from tumors of distant organs is not infrequently found but is usually overlooked, since macroscopic changes are not sharply outlined.

URETHRA

Carcinoma.—Robb,[46] in reviewing the literature, found that the lesion usually occurs deep in the bulbous urethra where it may arise

46. Robb, J. J.: Cancer of the Male Urethra: Report of Two Cases with a Short Survey of the Subject, Brit. J. Surg. **15**:605, 1928.

from Cowper's glands or from other glandular structure. The case reported by Robb is apparently the first one on record in which cancer of the urethra originated in a stricture. The patient, a man, aged 59, contracted gonorrhea at the age of 21. For six years he was treated for a stricture which had been dilated on 111 occasions, a total of 477 instruments having been passed. Eventually, it became impossible to pass instruments, and he was admitted to the hospital. A hard stricture could be felt at the penoscrotal angle, with a nodule about the size of a "small marble" on its upper and left side. The stricture was excised, and microscopic examination of the tissue revealed a transitional cell carcinoma. Further operation was refused at the time, but two and a half months later, on recurrence of the nodule, the patient consented to amputation. A case was reported also of a man, aged 69, who was admitted to the hospital with a suprapubic fistula following cystotomy. There was a dense mass in the perineum. A specimen removed revealed transitional cell carcinoma.

From seventy-six case reports from the literature in which evidence as to the nature of the tumor was available, the following list was compiled: squamous cell carcinoma, 73 per cent; columnar cell carcinoma, 1.5 per cent; papillary carcinoma, 3.5 per cent; adenocarcinoma, 21.2 per cent (from Cowper's glands), and transitional cell carcinoma, 1.3 per cent.

Great difficulty was experienced in determining the site of these tumors, owing to the insufficient data in the recorded cases. Robb, therefore, referred only to the sixty-one case reports found by Diehle and classified as follows: membranous urethra, thirty-three; pars cavernosa, twenty-six; and fossa navicularis, two. Recognition of the high percentage of squamous cell carcinomas which occur in the male urethra casts doubt on the small number originating in the fossa navicularis. Descriptions are inadequate to make this opinion decisive, but in a large proportion of cases in which the anterior part of the pars cavernosa is involved, the condition may originate in and around the fossa navicularis and thence spread backward.

Carcinoma of the urethra is rarely diagnosed in its early stages; most of the patients are treated for strictures of the urethra, and not until late in the course is the proper label affixed and adequate treatment begun. Robb expressed the belief that it would be true wisdom immediately to suspect every pathologic change toward the formation of tumor in the urethra as tending toward malignant disease and to treat it as such.

The symptoms of the disease may be divided into three stages. In the first stage, as in stricture, there is difficulty in urination because of the early obstruction by the tumor, a difficulty that is usually accompanied by urethral pain. Often there is a purulent or blood-stained

discharge. Retention of urine sooner or later occurs, and the picture immediately suggests simple stricture. The patient looks well but as a rule feels weak. This stage may exist for several months. In the second stage, a local tumor forms. In the third stage, infection is the predominating factor; periurethral abscess forms which, on bursting, results in fistula. In 80 per cent of the cases this fistula opens on the under surface of the penis.

Peters [47] stated that primary carcinoma of the male urethra is rarely encountered; there are less than 100 cases reported in the literature. Gonorrhea, stricture, leukoplakia or any other chronic inflammatory process is probably not of primary importance.

A case is reported of a patient, aged 42. The bladder was distended, and attempted catheterization met obstruction in the deep urethra. On incision, pus and urine were encountered in the tissues. The inflammatory portion seemed to be on the edges of a distinct mass of hard tissue which had not broken down, and sections taken for examination revealed epidermoid carcinoma.

Chute, in discussing Peters' paper, reported a case in which he made an opening into the urethra and curetted a cavity behind a urethral stricture. Fifteen years later, a mass in the left side of the perineum and a fistula near the penoscrotal angle were found. Some time later, Chute operated and removed a mass of hard tissue and a considerable portion of the left side of the urethra. Microscopic examination revealed carcinoma. A year later the patient returned, showing an area of recurrence entirely surrounding the urethra. Chute cut out a section of the urethra and sewed the ends together.

[COMPILER'S NOTE: Primary tumor of the urethra is extremely rare. In one series of 16,637 cases of tumors of various organs cited by Englisch,[48] no instance of malignant growth of the urethra was noted. In another series of 4,000 cases of disease of the male urinary organs, only 3 were of carcinoma of the urethra. In 358 cases of carcinoma of traumatic origin reviewed by Lowenthal,[49] there were 2 of carcinoma of the urethra.

Occasionally urethral carcinomas are preceded, as in Chute's case, by periods of urinary difficulty and irritation. The formation of tumor is somewhat analogous to the long-standing premalignant stages preceding the development of squamous cell tumors of the urinary bladder.

47. Peters, C. N.: Primary Epidermoid Carcinoma of the Male Urethra, New England J. Med. **199**:269, 1928.

48. Englisch, J.: Das Epithelium der männlichen Harnröhre, Folia urolog. **1**:38, 1907.

49. Lowenthal, Carl: Ueber die traumatische Entstehung der Geschwülste, Arch. f. klin. Chir. **49**:1 and 267, 1895.

König [50] reported a case of urethral carcinoma developing after urinary obstruction of forty-eight years' duration, and Oberlander [51] noted a somewhat similar case developing after forty years of urinary difficulty.

The onset may be quite rapid in young persons. Barney [52] and Fuller [53] both reported cases of sudden onset with acute retention. Schustler [54] reported a case of acute retention with fourteen days of uremia, followed by death. Most of these tumors occur at the usual site of the formation of the stricture. Of forty-two cases of carcinoma of the male urethra noted by Preiswerk,[55] thirty-eight were in the membranous or cavernous urethra.

Most of these carcinomas have a histologic structure similar to that of squamous cell epithelioma of the penis, although of a higher degree of malignancy. Metastatic growths, which are not common, have the same tendency to remain localized in the primary glands as do those arising from epitheliomas of the penis. At times the only symptoms are those resulting from moderate obstruction, together with marked hematuria, especially after urethral manipulation.

Diverticula.—Mouat [56] stated that urethral diverticula may be congenital or they may be acquired. Those in the prostatic urethra are most commonly acquired from the gradual increase in size and communication with the urethra of a sac containing prostatic calculi. In a less common type, the prostatic urethra may gradually become distended to form a sac as a result of the lodgment of stones in that portion of the canal. Mouat reported a number of interesting cases. In one a 2 ounce (56.7 Gm.) stone was found in a sac which communicated with the posterior urethra. At operation, the stone was cut down on from the perineum. It was deeply grooved on the surface, corresponding to the gap in the floor of the urethra. The pouch was excised, and the edges of the urethral opening were stitched together over a catheter inserted into the bladder.

In the anterior urethra, the acquired type of diverticula is much more common than the congenital variety. A case is described of a stone

50. König: Cancroid des Bulbus und der Pars nuda urethrae, Monatsbl. f. Urol. **6**:641, 1901.

51. Oberlander, F. M.: Beitrag zur Lehre vom primären carcinoma urethrae, Internat. Centralbl. f. d. Physiol. u. Path. d. Harn. u. Sex-Org. **4**:244, 1893.

52. Barney, J. D.: Cancer of the Male Urethra: Report of Two Cases, Boston M. & S. J. **157**:790, 1907.

53. Fuller, E.: Six Successful and Successive Cases of Prostatectomy, J. Cutan. & Genito.-Urin. Dis. **13**:229, 1895.

54. Schustler, M.: Ueber einen Fall von Epithelil carcinoma in der Kontimutät der männlichen Harnrohre, Wien. med. Wchnschr. **31**:157, 1881.

55. Preiswerk, P.: Ueber das primäre Karzinom der männlichen Urethra, Ztschr. f. Urol. **1**:273, 1907.

56. Mouat, T. B.: Urethral Diverticula, Brit. J. Surg. **16**:51, 1928.

in a pouch which communicated with the floor of the urethra at the penoscrotal juncture. The stone was cut down on, under local anesthesia, and removed from the thin-walled sac, which was tightly stretched over it. A small opening which communicated with the urethra was stitched up, and the thin-walled sac was obliterated.

In forty cases of acquired diverticula of the urethra, there was a history of a previous operation on the urethra in sixteen; in the remainder, false passages, blows or falls on the perineum and periurethral abscesses are stated as possible causes of the condition.

The diagnosis of a pouch opening into the anterior urethra is as a rule easily made, as the stones which are usually contained in the sac can generally be felt in the perineum. When the sac is not fully occupied by calculi, it may become distended during the act of micturition. The diagnosis is more difficult if the diverticulum is connected with the posterior urethra, although with present day urologic technic it is possible to fill the pouch with a substance that will cast a shadow and which readily outlines the diverticulum.

Calculi in the prostate gland give rise to a sense of weight, pain and irritation in the perineum and sometimes to retention of urine. Crepitation, which may be felt by the examining finger in contact with stones in a pouch, is characteristic and has been compared to "beads in a bag."

When it is possible, an attempt should be made to dissect out the wall of the sac, after it has opened and emptied of its contents. The aperture of communication with the urethra may be closed by suturing lateral flaps, which have been dissected up at the neck of the sac. Usually the most that can be done in the acquired forms of prostatic diverticula is to cut down and evacuate their contents by a median perineal section, a procedure that is sometimes followed by a reformation of stones.

McKay and Colston [57] found that reported cases of diverticula of the urethra are rare and that in only a few are methods of treatment given. The symptoms of urethral diverticula depend on the site, size, depth and degree of infection. The most obvious symptoms are deep-seated pain in the perineum, dysuria and dribbling at the end of urination. A diverticulum of the anterior urethra often presents a fluctuating tumor that fills during the act of urination and is easily emptied by pressure. A diagnosis is usually made by means of the cysto-urethroscope and the roentgen rays, and the transitory subsiding tumor is occasionally seen.

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57. McKay, R. W., and Colston, J. A. C.: Diverticula of the Male Urethra, Surg. Gynec. Obst. **48**:51, 1929.

If the diverticulum is to be resected, an incision is made over the diverticulum through the skin and subcutaneous tissues. It is then freed by sharp and blunt dissection. It is resected close to its entrance into the urethra, and its stump is turned into the urethra by a purse-string suture, similar to the manner in which the stump of the vermiform appendix is turned in. The purse-string suture is reinforced by bringing the surrounding tissues over by means of mattress sutures. The bladder is drained by an inlying catheter through the urethra; the operative area is not drained, but skin and subcutaneous tissues are closed by fine silk or silver clips.

Another operative procedure described by McKay and Colston is opening the diverticulum into the prostatic urethra, thus making one cavity. This method is applicable only to the diverticula found in the posterior or prostatic urethra. A perineal or suprapubic approach is used with the idea of removing the roof from the diverticulum and converting the cavity of the diverticulum and the cavity of the prostatic urethra into one common opening. This insures proper drainage and also obviates obstruction to urination.

In ten reported cases, seven patients were treated by operative procedures, and one was treated by the injection of silver nitrate. Two patients refused treatment. Only one case was complicated by stone. In the seven cases in which operation was performed, complete resection was done in five, followed by closure of the defect in the urethra over a soft rubber catheter. In four of five patients treated by resection, the diverticula occurred in the anterior urethra, and in one, in the posterior urethra just behind the external sphincter.

Epispadias.—Davis [58] observed that success has been attained in practically every case in which the surgical procedures in the treatment of epispadias in the female have been properly planned and executed. He stated the belief that it is unnecessary to subject the patient to the risk of ascending renal infection, which is always present after this operation.

Davis employed a two-stage procedure, the second step of which is usually not necessary when the first one is properly carried out. The first stage consists of thoroughgoing plastic repair of the defect. He made a wide exposure of the affected areas, and sufficient and thoroughly controlled excision of excessive mucosa was done under vision. It is important to cut the urethra small enough; if it is too small it can easily be dilated, but if it is too large the operation is a failure and must be repeated. Care should be used in suturing the halves of

58. Davis, D. M.: Epispadias in Females and Its Surgical Treatment, J. Urol. **20**:673, 1928.

the defective internal sphincter muscle over the anterior aspect of the newly formed vesical orifice. The urine should be diverted by a drainage tube in the bladder during the period of healing. If the first step should fail, Deming's gracilis muscle plastic operation is performed. Davis expressed the belief that these methods can be relied on to produce a cure in practically every case of epispadias in the female.

MALIGNANT DISEASE OF THE URINARY TRACT

Barney [59] stated that hematuria is the most common and often the earliest symptom of malignant disease of the urinary tract. It may be microscopic or macroscopic. It cannot be influenced by medication, and it may not reappear for weeks or months. Pain is not an outstanding feature of malignant disease in this region. It occurs generally at a late stage in the disease and is frequently felt in places other than the primary source. Metastasis from prostatic carcinoma occurs early and often, from the kidney later and less frequently and from the bladder, late and seldom. About one fifth of all cases of prostatic obstruction are associated with carcinoma of the prostate gland. It may not give rise to urinary symptoms.

Early diagnosis of malignant disease of the urinary tract is made with disappointing infrequency, because of the fact that it does not cause outstanding symptoms until well advanced.

URINARY INFECTION

Schlack [60] reported that in cultures made from 350 specimens of urine of eighty infants, 45 per cent remained sterile. In the nonsterile group, colon bacilli were found in one-third and cocci in the remaining two-thirds. In spite of the finding of bacteria, there was no pyuria. The pyuria may begin with bacteriuria or with symptoms of nephritis.

Experimental and clinical observations on the dehydration types of pyuria are noted but not considered as true infection. They are recognized as renal symptoms, since there are no bacteria present and the cells in the urine are mainly mononuclears, which Schlack assumed came from the renal tubules. In many cases, in spite of early pyuria, the sediment contains mostly mononuclears. Doubtless these cells in the urine are epithelial in origin. Microscopic study of the kidney supports this view.

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59. Barney, J. D.: The Early Diagnosis of Malignant Disease of the Urinary Tract, New England J. Med. **199**:281, 1928.

60. Schlack, Hans: Zur Pathogenese der Pyurie, Jahrb. f. Kinderh. **118**:224, 1927; abstr., Ztschr. f. urol. Chir. **24**:363, 1928.

EXTRAVASATION OF URINE

Soloway [61] stated that extravasation of urine is an emergency condition demanding immediate surgical attention. It is caused by stricture of the urethra in most cases and is usually accompanied by a periurethral abscess. In cases of extravasation in which there is no obstruction to urinary outflow, the anaerobic organisms are significant etiologically. The course of the extravasated urine is determined by the relationship between the point of rupture of the urethra and the fascial planes of the perineum. The most common site of rupture is the bulbous urethra, then the membranous urethra, and rarely the prostatic urethra. The physical state of the urine at the time of rupture was observed to play an important part in the course of the condition. Soloway expressed the belief that the best results are obtained by radically opening the focus of infiltration with wide incisions and by rectifying the stricture, when present. Both of these procedures should be done at the same time. Spinal anesthesia has given satisfactory results.

Streptococcus scrotal and penile gangrene and idiopathic gangrene of the scrotum are conditions which closely resemble extravasation and from which it must be distinguished. The prognosis depends on early diagnosis, the duration of the extravasated urine, and immediate radical operation.

URINARY ANTISEPTICS

Voit [62] conducted experiments to determine whether or not the body disposes of methenamine mainly through the urinary tract or by other means. He found that in the oral administration of methenamine (from 2 to 200 Gm.) free formaldehyde is formed within fifteen minutes; in hyperacidity, it occurs in correspondingly greater amounts. It is to be assumed that this formaldehyde may be lost as far as therapeutic value is concerned, as it is not always found in the urine. Methenamine administered intravenously yields greater quantities and for that reason is found more often in the urine as free formaldehyde.

Further research and animal experimentation have shown that it is excreted by the liver. Voit also showed that it may be excreted by the skin. From these data he concluded that if any therapeutic value is to be obtained by its administration by mouth, large quantities must be given.

FUNCTIONAL TESTS

Bugbee [63] stated that renal function is one of the most vital factors influencing the treatment for urologic surgical conditions. Subsequent

61. Soloway, H. M.: Extravasation of Urine, J. Urol. **20**:569, 1928.

62. Voit, K.: Untersuchungen über die Ausscheidung von Urotropia, abstr., Ztschr. f. urol. Chir. **24**:327, 1928.

63. Bugbee, H. G.: The Rôle of Kidney Function in Urologic Surgery, J. Urol. **20**:541, 1928.

to operation, a continuous knowledge of renal function is of decided value in checking off the progress, estimating the prognosis and influencing the future conduct of the case. Such knowledge is particularly applicable in cases of prostatic obstruction, in which, due to back pressure on the kidneys, congestion soon gives way to renal injury. Dating from the time when regional anesthesia was adopted as a routine measure, in a series of 171 consecutive cases of prostatic obstruction in which treatment was by open operation, only 1 patient (the one hundred and twenty-seventh) died.

Combined estimations of the chemical constituents of the blood and phenolsulphonphthalein have been found satisfactory in determining renal function, but the limitations of either when employed alone have been demonstrated. The observation of a persistently high blood urea has indicated poor renal function. Under reduced protein diet and forced fluids it has been observed that the blood urea often recedes rapidly, while the phenolsulphonphthalein output remains low. In these cases estimations of blood urea alone are of little value, or in combination with the phenolsulphonphthalein test should not influence one against the evidence produced by the phenolsulphonphthalein elimination.

Bugbee attempted to maintain as closely as possible a renal balance throughout. Necessary preliminaries to this end are slow decompression of the bladder, should the residual average be more than 300 cc., and drainage with the indwelling catheter until the function has been stabilized under the relief of back pressure. Bugbee expressed the belief that the type of procedure used in cases of benign hypertrophy of the prostate gland is mainly a matter of personal choice for the operator to decide in the particular case. In his series, if there was the slightest doubt as to the advisability of preliminary cystostomy, this procedure was instituted. In 5 of the 171 cases perineal prostatectomy was done, and in 5, suprapubic prostatectomy in one stage. In 2 cases of carcinoma, only permanent suprapubic drainage was established. In 8 cases a punch operation was adequate after preliminary cystostomy, the prostate gland having become reduced to such an extent that only a fibrous ring remained. Enucleation through a drainage wound is seldom difficult; in none of Bugbee's series was enucleation incomplete or tabs left to interfere with function. There is less tendency to hemorrhage following enucleation after cystostomy drainage, and it is more easily controlled with the hemostatic bag than after the single operation.

Only 4 operative deaths occurred in 181 consecutive operations on the kidney. With due credit to the significance of the early and correct diagnosis of renal lesions, Bugbee considered that a higher mortality was prevented by continued study of the affected kidneys, which largely governed the management of the cases.

TESTS OF RENAL FUNCTION

Maxwell[64] referred to a study made by MacAdam and Shiskin who found that the cholesterol content of the plasma appears to be a fair measure of the degree of the individual resistance to infection. Such estimations form a useful guide to the degree of operative risk in cases of urinary obstruction. Assuming the lower limit of the plasma cholesterol in health to be 0.13 Gm. per hundred cubic centimeters, they found that of eighteen patients with values below this limit, sixteen died of pyelonephritis and only two recovered. Of the seventy patients with cholesterol values above 0.13 Gm. per hundred cubic centimeters, eleven died, in only one of whom was death a result of ascending urinary infection. It was also noted that, in a large proportion of the cases in which low cholesterol value was found, the clinical condition did not contraindicate operation, and such clinical evidence as there was depended on some degree of defect in renal function rather than on the latent sepsis, from the effects of which the patients ultimately succumbed. MacAdam and Shiskin considered that the test is of much less value in cases of malignant disease, the cholesterol figure being frequently high even when pyelonephritis coexists. Maxwell pointed out that there is a wide variation in the cholesterol content of presumably normal blood figures, varying from 0.08 to 0.23 per hundred cubic centimeters. In this respect it must be clearly recognized that the interpretation of the results of determination of plasma cholesterol differs considerably from that of the other common chemical examinations of the blood. The blood urea and blood sugar have much less variable normal values, and neither is so liable to be affected by a multitude of external factors, partly recognized but still partly unknown, as is the plasma cholesterol. Of five patients with low cholesterol values and who should have been bad risks, two died and three recovered; whereas, of twelve patients with normal cholesterol values, four were clinically unfit for any operation. Three of the remaining eight patients died. Maxwell stated that these results do not bear out the claims of MacAdam and Shiskin as to the significance of the plasma cholesterol from a prognostic point of view.

The chief difficulties in the interpretation of the results appear to be the wide range of variation which may be observed in normal persons and the consequent impossibility of gaging the level in health for any given case. Acute retention of urine appears to have considerably more effect in lowering the plasma cholesterol content than is realized at present, so that deductions should not be drawn from results obtained only previous to the relief of the obstruction.

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64. Maxwell, James: The Significance of the Blood-Cholesterol in Genito-Urinary Surgery, Brit. J. Surg. **16**:226, 1928.

The impression gained was that clinical observation, combined with observations on blood urea and urea concentration, yielded in most cases a reasonably accurate forecast of future events. On several occasions a low plasma cholesterol content suggested a bad prognosis, which did not materialize, whereas other patients with normal cholesterol values but who were bad operative risks clinically were either refused operation on clinical grounds alone or died shortly thereafter as a result of some complicating infection.

It would seem that owing to the present rudimentary state of knowledge concerning the cholesterol content of the blood plasma, it is impossible to achieve an accurate summing up, with consequent enlightenment, from the consideration of any individual case. Maxwell expressed the belief that what is really needed is a more intensive study of the normal values obtained in healthy persons, a more complete investigation of the factors causing changes in the plasma cholesterol, and a closer study of cholesterol values and of cholesterol curves in different pathologic states. It would be unjust to refuse operative assistance to any patient suffering from the effects of urinary obstruction merely because on one occasion previous to the proposed operation a low plasma cholesterol value had been reported. Such results are extremely likely to be equivocal, and interpretation is open to fallacy.

(To be continued)

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